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CHANGES IN THE FUNDUS OCULI AS A DEFINITE INDEX TO ARTERIAL DISEASE

ANALYSIS OF ONE HUNDRED CASES *

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It is universally recognized that marked changes of the retinal arteries are associated with changes in the organs, particularly in the kidneys. That changes in the fundus can be found in general arteriosclerosis and in interstitial nephritis in their incipiency, and that such changes are synchronous with corresponding changes in the kidney and other organs, has not been sufficiently emphasized. While much has been written, the trouble has been that the ophthalmologist has not delved deeply enough into the medical aspect, and the internists are not sufficiently keen with the ophthalmoscope.

It is my contention that sclerosis of the arterioles of the kidney and brain cannot exist in the absence of a similar condition of the retinal arteries, and normal retinal vessels definitely exclude interstitial nephritis of the sclerotic type (small contracted kidney). Nephritis, or "nephrosis," such as is encountered following one of the infectious diseases, or possibly is caused by focal infection and is characterized by considerable albuminuria, may exist without arterial disease. The fundus in these cases may be normal or may sometimes show albuminuric neuroretinitis without any, or with slight, sclerotic changes in the retinal arteries. To support this theory, I have compiled a number of cardiovascular cases from the medical service of Montefiore Hospital with a study of blood pressure, blood chemistry and kidney function in relation to the appearance of the fundi.

Changes in the retinal arteries correspond to the degree of development of arterial disease in the organs and in the brain. To facilitate their recognition, I have numbered them in the order of their usual appearance, as pointed out in a previous paper.

(1) Increased light reflex. In young persons, the light falling on the arteries and veins creates a white line coursing unsteadily on top of the vessels. This is a manifestation of what is known as juvenile reflex, and is accompanied by a silvery shimmer of the retina. Older patients with normal arteries show only a slight reflex.

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* From the Medical and Neurological Service of Montefiore Hospital.

(2) Reflex more marked. The color and caliber of the arteries is unchanged, but there is a slight pressure effect on the veins. By the latter is meant the effect on the outline of the vein as a sclerotic artery passes over it. In proportion to the degree of sclerosis, the lumen of the vein is attenuated, or the vein may actually disappear for a short distance as it passes under the artery. In this second degree, there is only a slight narrowing of the vein.

(3) Copper wire arteries. The arteries become slightly narrower than normal, somewhat uneven in caliber and decidedly paler. Pressure effect on the veins is marked.

(4) The same as (3) with tortuosities of the small branches of the arteries and veins, particularly in the region between the disk and the macula.

(5) The same as (3) and (4), with marked tortuosities with small hemorrhages and exudates.

(6) Perivasculitis, with occlusion of small branches.

(7) Edema of the disk with larger exudates and hemorrhages, atrophy of the retina, with low grade pigment proliferation.

Blocking of the central retinal artery is most likely to occur in arteriosclerosis of the second or third degree.

Moderate sclerosis of the retinal blood vessels may be accompanied by advanced sclerosis of the choroidal blood vessels. The vessels of the choroidal mosaic become pale and sharply defined. Visibility of the choroid is due to atrophy of the pigment epithelium.

The average blood pressure corresponding to that in (1) is normal; in (2), 150 to 160; (3), 170 to 180; (4), 190 to 200; (5), over 200.

The early changes are frequently unnoticed, and the results of the examination of the fundus are called negative. In the absence of changes in the retinal arteries, high blood pressure is most likely functional, and the kidney, normal.

The first most important definite sign is the pressure effect on the veins. This is usually accompanied by pale copper wire arteries. In the presence of some pressure effect, with large arteries of good color, there is no elevation of blood pressure. In examination for life insurance, a careful scrutiny of the fundi would yield the examiner considerably more information than just taking the blood pressure. The latter can be temporarily reduced by a starvation diet; even the urine can be freed from a trace of albumin, but the appearance of the fundus is constant. I would, for instance, consider a man, 50 years of age, with normal retinal arteries, a good risk in the absence of any surgical pathologic condition. On the other hand, a patient showing change (2) in his retinal arteries would surely be a poor risk, even though normal otherwise. His arteriosclerosis is apt to progress; he may develop blocking of a cerebral artery or vein or even blocking of the coronary artery. This inference is drawn from the occurrence of so many cases of hemiplegia and angina without high blood pressure, endocarditis or syphilis. Severe attacks of cerebral apoplexy are more frequent in patients without high blood pres-

sure, and are usually unexpected. A careful examination of the fundus in these cases would disclose incipient arterial disease.

What may occur in cerebral arteries and veins can be visualized in cases of blocking of the central retinal arteries and veins. A good demonstration of what may happen was seen in a patient who came to the New York Eye and Ear Infirmary, Dr. Shine's service, with a blocking of the central artery. While his blood pressure, which was found to be 160 systolic, was being taken, he developed a hemiplegia.

Clinicians, as a rule, will distinguish between attacks of "stroke" in the presence of low blood pressure and apoplexy in the presence of high blood pressure. They ascribe the former to thrombosis of the cerebral artery or its branches, and the latter to hemorrhage caused by rupture of a cerebral artery. Patients with high blood pressure are more apt to have hemorrhage from the smaller branches of the arteries or veins, or else they may have blocking of the smaller branches, as in the presence of high blood pressure they are not likely to develop a thrombosis in the larger trunks unless the disease is far advanced, because the high blood pressure creates a strong "vis a vergo."

When one sees what happens in the retina as a result of thrombosis of the central vein, i.e., large hemorrhages, it seems to me that in the presence of moderate elevation of blood pressure or low blood pressure a similar accident may occur in the brain. Of course, free collateral venous circulation of the brain must be taken into consideration. A thrombosis of the central artery results in atrophy of the retina; in the brain, blocking of a cerebral artery results in softening of the brain. The extent of the disease depends on the size of the blood vessel which was blocked. It would seem logical to come to the conclusion that severe attacks of apoplexy with hemiplegia are not always caused by hemorrhage from a ruptured artery, but may be caused either by thrombosis of a large artery or vein in the absence of high blood pressure or in the presence of a rapid drop in blood pressure, such as might be caused by shock with weakened heart action. In fact, strong doubts may be entertained as to the frequency of rupture of larger branches of arteries. These conclusions are drawn merely from careful study of the behavior of the retinal arteries. I have never seen a rupture of the retinal artery, except at the terminals. Atheroma of the arterial wall, I believe, occurs only in the larger arterial trunks.

Further study of the retina disclosed that cases of peripheral arteriosclerosis, such as is found in old people, is not necessarily associated with changes in the retina. Patients with this condition may have a normal blood pressure and normal kidney function, and longevity is not affected. This observation may again he visualized in the eye, where peripheral arteriosclerosis, while not affecting the retinal blood vessels, is often marked by sclerosis of the choroidal blood vessels, with secondary

Observations in Cases of Arterial Disease

Name	Age, Years	Sex*	Diagnosis	Estimated Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg. per 100 Cc.	Urine	Retinal Changes
D. T.	63	♂	Advanced arteriosclerosis; cardiac decompensation and insufficiency	170-180	170/100 206/100	4,660,000; hemoglobin, 85%	Urea nitrogen, 30.1; sugar, 129	Faint trace of albumin	(3); arteriosclerosis
R. W.	45	♀	Diabetes; general arteriosclerosis; cardiac hypertrophy; hemiplegia	160	162/ 80	4,080,000; hemoglobin, 75%	Urea nitrogen, 11.5; sugar, 337; cholesterol, 170	Sugar, negative; albumin, negative	(2)
J. R.	46	♂	Hypertension; arteriosclerosis; cardiac hypertrophy and dilatation; mitral insufficiency; hydrothorax; ascites; arrhythmia	160	175/125 180/116	5,100,000; hemoglobin, 75%	Urea nitrogen, 15.1; sugar, 86	Trace of albumin	High degree of myopia; sclerosis of choroidal blood vessels; retinal blood vessels; (2)
M. S.	46	♀	Hemiplegia	200+	150/140	S———	Urea nitrogen, 32.5; sugar, 105	Albumin, 3+	(7)
A. P.	54	♂	Auricular fibrillation; hypertension	160	109/126 226/128	5,210,000; hemoglobin, 95%	Urea nitrogen, 18.6; sugar, 110	Sugar, +; albumin, negative granular casts	(2)
S. C.	54	♀	Chronic neuritis	Normal	126/ 78	4,300,000; hemoglobin, 80%	Urea nitrogen, 10.9; uric acid, 2.5; sugar, 100	Negative	High degree of myopia; (1)
S. W.	50	♂	Mitral stenosis and insufficiency; general arteriosclerosis; cardiac hypertrophy; arrhythmia	160-170	160/ 70	.....	Urea nitrogen, 17.6; sugar, 121	Negative	(2); Drusen
J. S.	57	♂	Mitral insufficiency; chronic nephritis ?	160	1921 190/ 90 160/100	.....	.....	Negative	(2)
N. F.	57	♂	Cerebral hemorrhage; encephalomania; arteriosclerosis; cardiac hypertrophy and dilatation	190-200	200/130	.....	.....	Negative	(4)
L. D.	53	♂	Obesity; syphilis; aortitis; aortic insufficiency	180	124/ 62	.....	Urea nitrogen, 14.7; sugar, 118	Negative	(3)
B. K.	55	♀	Diabetes; chronic nephritis; aortic dilatation and insufficiency; arteriosclerosis	200	210/ 80	2,320,000; hemoglobin, 40%	Urea nitrogen, 27.3-88.9; sugar, 122-150	No albumin, but many granular casts	(5)
J. S.	54	♂	Diabetes; multiple neuritis; general arteriosclerosis; one leg amputated	160	136/ 60 168/ 72	4,224,000; hemoglobin, 70%	Urea nitrogen, 17.8; sugar, 196; cholesterol, 183	Trace of albumin, otherwise negative	Arteriosclerosis; (2); diabetic retinitis
H. R.	47	♀	Chronic pulmonary tuberculosis; incipient hypertension; cardiac hypertrophy	160	156/ 86	.....	.....	.....	Right eye, very narrow arteries as if partially occluded, macula darker than normal; left eye, opacity of cornea, narrow arteries
R. B.	57	♀	Diabetes; hypertension; cardiac hypertrophy; cholecystitis	160	166/ 78	.....	Urea nitrogen, 7.4; sugar, 192	Trace of sugar	(2)

Y. K.	50	..	Diabetes; cerebral arteriosclerosis; aphasia	190-200	170/ 94 192/ 86	.....	Urea nitrogen, 16.8; sugar, 252; cholesterol, 141	Dextrose plus albumin, trace; a few granular casts	(4)
I. G.	65	♀	Coronary arteriosclerosis; general arteriosclerosis	150-160	148/ 82	4,960,000	Urea nitrogen, 11.9; sugar, 104	Negative	(2); coronary attacks probably caused by contraction of artery
S. G.	64	♀	Hypertension; cerebral thrombosis; (essential hypertension)	160	220/145	3,800,000; hemoglobin, 80%	Urea nitrogen, 31.6; sugar, 157	Negative	(2)
H. C.	66	♀	Left hemiparesis	180	190/110	.....	Urea nitrogen, 11.2; sugar, 124	Trace of albumin; granular casts	(3)
M. W.	51	♀	Left hemiplegia; chronic endocarditis; cerebral embolism; arteriosclerosis	200+	220/145 310+/150	3,000,000; hemoglobin, 65%	Urea nitrogen, 10.3; sugar, 97	Trace of albumin	Right eye, plus; left eye, glaucomatous cupping; (5); arteriosclerosis
J. C.	48	♀	Diabetes; arteriosclerosis.....	Normal	120/ 80	4,848,000	Urea nitrogen, 12.6; sugar, 155; cholesterol, 176	Negative	(1)
B. K.	59	♂	Left hemiplegia; cerebral thrombosis	150-160	150/ 80 120/ 80	.....	Urea nitrogen, 42.5; sugar, 178 May 11, 1926, urea nitrogen, 14.7	Albumin, 4 plus; no casts	(2); arteriosclerosis; case of nephrosis
M. E.	58	♂	Postencephalitic condition...	150-160	152/100	Normal	Normal	Negative	(2)
I. G.	49	♂	Hypertension; right hemiplegia	170-180	170/100	.....	.....	Negative	(3)
P. K.	59	♂	Arteriosclerosis; tumor of the spinal cord	160	165/105	.....	.....	Negative	(2)
P. L.	60	♂	Aortic insufficiency; auricular fibrillation	150	210/ 88	.....	Urea nitrogen, 21; sugar, 97	Albumin, 4 plus	(1)
S. P.	49	♀	Postencephalitis; parkinsonian syndrome	170	130/ 80 160/ 80	4,660,000; hemoglobin, 85%	Urea nitrogen, 16.5; sugar, 107	Negative	Arteriosclerosis; (2); arteries narrow
B. B.	49	♂	Polycytemia; hypertension; general arteriosclerosis; angina pectoris; neurasthenia	170-180	218/216	7,800,000; hemoglobin, 130%	.....	Negative	(3); macular degeneration
A. W.	82	♀	Hypertension	180	206/110 265/140	.....	Urea nitrogen, 16.5; sugar, 133	Trace of albumin; granular casts	(3); sclerosis of choroidal blood vessels; peripapillary atrophy
J. S.	61	♂	General arteriosclerosis and hypertension; hemiplegia; emphysema and bronchitis; cardiac hypertrophy and dilatation	200+	200/110	5,760,000; hemoglobin, 100%	.....	Negative	Narrow, pale arteries
A. T.	61	♀	Chronic nephritis; hypertension; cardiac dilatation	200+	168/ 85 250/150	2,880,000; hemoglobin, 58%	Urea nitrogen, 58; creatinine, 4.36	Albumin, 3 plus	(5); plus
H. D.	57	♀	Diabetes mellitus; peripheral neuritis	140	142/ 8	6,100,000; hemoglobin, 90%	Urea nitrogen, 12.3; sugar, 273; cholesterol, 133	Negative	(1); plus
S. R.	63	♂	General arteriosclerosis and atherosclerosis; dilatation of aorta; cardiac hypertrophy and dilatation	160	154/ 80	5,200,000; hemoglobin, 85%	.....	Negative	(2)

* In this table, ♂ indicates male; ♀, female.

Observations in Cases of Arterial Disease—Continued

Name	Age, Years	Sex*	Diagnosis	Estimated Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg. per 100 Cc.	Urine	Retinal Changes
A. S.	60	♂	Diabetes; hypertension	150	172/100	hemoglobin, 88%	Urea nitrogen, 15.6; sugar, 276-307	Trace of sugar	Diabetic retinitis with hemorrhage and exudates
O. R.	71	♂	Emphysema and chronic bronchitis	Normal	102/ 60 118/ 86	.....	.....	Negative; a few hyaline casts	(1)
R. R.	63	♂	Right hemiplegia; general arteriosclerosis	160	140/ 70 190/110	.....	Urea nitrogen, 14.4; sugar, 178	Negative	(2)
S. R.	62	♂	Left hemiplegia	200	188/126 212/126	.....	Urea nitrogen, 13.7; sugar, 115	Negative	(5)
H. B.	39	♂	Hemiplegia; emphysema	Normal	170/124 140/ 85	4,920,000; hemoglobin, 90%	Urea nitrogen, 14; sugar, 105	Negative	(1)
S. H.	52	♂	Myocarditis; hypertrophy; dilatation; general arteriosclerosis; nephritis	160-170	142/ 88 172/120	.....	Urea nitrogen, 28.7; sugar, 96	Albumin, 2 plus; granular casts	(2); plus; sclerosis of choroidal blood vessels
J. W.	61	♂	Hemiplegia	150	90/ 58 156/100	.....	Urea nitrogen, 15.4; sugar, 100; uric acid, 2.2	Negative	(1); plus
H. S.	73	♂	Dilatation of aorta; atherosclerosis; extrasystoles; general arteriosclerosis	160	170/ 85 185/100	.....	Urea nitrogen, 22.8; sugar, 122; uric acid, 2.4	Trace of albumin; hyaline casts	Retinitis like diabetic arteriosclerosis; (2)
L. P.	57	♂	Right hemiplegia	170	170/ 95 178/ 94	4,100,000; hemoglobin, 80%	Urea nitrogen, 15.9; sugar, 121	Negative	(2); plus
C. S.	60	♂	Multiple cerebral hemorrhage	200	136/ 94 154/100	.....	Urea nitrogen, 24.2; sugar, 133	Trace of albumin	(5)
J. D.	49	♂	Right hemiplegia; hypertension; aortitis	190	195/120 164/124	4,712,000; hemoglobin, 88%	Urea nitrogen, 11.9; sugar, 109	Trace of albumin	(4)
I. P.	66	♀	Central tumor.....	190	185/100	.....	Urea nitrogen, 11.9; sugar, 113	Trace of albumin	(4); degenerative changes in the macula; disks hyperemic
M. S.	45	♂	Tabes dorsalis	170	120/ 80 156/ 96 186/122	3,450,000; hemoglobin, 78%	Urea nitrogen, 26.2; sugar, 108	Wassermann 2 plus	Simple primary optic atrophy; disseminated chorioretinitis; arteries (2); plus
B. W.	55	♂	Aortic and mitral insufficiency; coronary disease; hypertension	160/70	166/ 82 172/ 86	5,600,000; hemoglobin, 78%	Urea nitrogen, 8.4; sugar, 103	Albumin, 3 plus; hyaline and granular casts	(2); plus
R. L.	52	♀	Hypertension; cardiac hypertrophy and dilatation; chronic nephritis	200+	240/136 255/130	3,200,000; hemoglobin, 66%	Urea nitrogen, 80.6; sugar, 120; creatinine, 9.1	Albumin, 3 plus; hyaline casts	(6)
G. E.	40	♀	Hypertension; general arteriosclerosis; endocrine disease	High ?	155/105	4,900,000; hemoglobin, 95%	Urea nitrogen, 15.9; sugar, 97	Slight trace of albumin	Right eye, narrow and pale arteries, disk pale; left eye, narrow arteries, good color
B. B.	59	♀	Hemiplegia; hypertension	200+	194/110	.....	.....	Slight trace of albumin	(4) and some perivasculitis

B. B.	58	♀	Hypertension; hypertrophic emphysema; hemiplegia	150	230/130	.....	Urea nitrogen, 14; Uric acid, 3.7; sugar, 103; cholesterol, 270	Negative	(1); arteries normal in color but seem contracted in places; essential hypertension
A. M.	60	♂	Diabetes; advanced general arteriosclerosis	Normal	124/ 60 135/ 70	3,848,000; hemoglobin, 75%	Urea nitrogen, 11.5; sugar,, 198; cholesterol, 158	Sugar, 3 plus	(2)
R. N.	47	♀	Hemiplegia; hypertension; general arteriosclerosis; cardiac hypertrophy and dilatation	Elevated ?	196/130	4,700,000; hemoglobin, 85%	Urea nitrogen, 13.4; sugar, 137	Albumin, plus; hyaline and granular casts; specific gravity, 1.028	Arteries pale and narrow; no other change
P. M.	55	♂	Emphysema; general arteriosclerosis; relative mitral insufficiency	200	210/120	.....	Urea nitrogen, 23; sugar, 106	Slight trace of albumin	(6)
I. S.	55	♂	Right hemiparesis; syphilis ?.	200+	244/130	3,600,000; hemoglobin, 67%	Urea nitrogen, 21.6; sugar, 106	Negative; Wassermann negative	(7)
I. I. Weight, 300 pounds	58	♀	Essential hypertension	Normal	210/100 150/ 80 160/ 85	5,200,000; hemoglobin, 100%	Urea nitrogen, 10.3; sugar, 105	Negative	(1)
S. F.	65	♀	Cancer of left breast; metastases	160-170	170/ 80	.....	.....	Negative	(2); plus
M. C.	58	♂	Hypertension; general arteriosclerosis	180-190	219/110 250/138	.....	Urea nitrogen, 13.3; sugar, 104	Trace of albumin	(3); arteries very narrow
M. B.	66	♂	Left hemiplegia	Normal	136/ 66 140/ 70	.....	Urea nitrogen, 13.2; sugar, 132	Negative	(1)
A. K.	68	♂	Right hemiplegia	170	160/100	4,800,000; hemoglobin, 85%	Urea nitrogen, 14.7; sugar, 116	No specific gravity obtainable	(3); opacity; vitreous degenerative changes; left eye, evidence of blocking of retinal artery
H. M.	54	♂	Right hemiplegia	160	130/ 48 170/ 70	.....	.....	Negative	(2)
N. H.	74	♀	Cardiac hypertension and dilatation; mitral insufficiency; hypertension; chronic nephritis; hemiplegia; aphasia	180	180/ 95	.....	.....	Negative	(3)
B. G.	55	♀	Hypertension; chronic nephritis; cardiac hypertrophy; essential hypertension	160	174/ 86 200/ 98	3,190,000; hemoglobin, 78%	Urea nitrogen, 17.5; sugar, 100	Negative	(2)
A. F.	56	♂	Postencephalitic; parkinsonian syndrome	Normal	120/ 90	.....	.....	Negative	(1)
M. T.	58	♂	General arteriosclerosis; cardiac hypertrophy and dilatation; hypertension; intermittent claudication	160	154/ 88	4,330,000; hemoglobin, 85%	.....	Negative	(2); changes in macula
D. R.	52	♀	Hypertension; cardiac decompensation; cerebral hemorrhage	200+	236/120	4,520,000; hemoglobin, 75%	Urea nitrogen, 27.4; uric acid, 4.7; sugar, 99	Negative	(5)
R. W. Path.	53	♀	Cardiac hypertension and dilatation; left hemiplegia; arrhythmia; atheroma of aorta	200+	300/140	.....	Urea nitrogen, 9.2; uric acid, 4.2; sugar, 121	Casts and good trace of albumin	(5)

* In this column, ♂ indicates male; ♀, female.

Observations in Cases of Arterial Disease—Continued

Name	Age, Years	Sex*	Diagnosis	Estimated Blood Pressure	Measured Blood Pressure	Red Blood Count	Blood Chemistry, Mg. per 100 Cc.	Urine	Retinal Changes
S. W.	59	♀	Carcinoma of pleural cavity; mitral insufficiency; hypertension	160	165/95 to 212/140	.....	Normal	Albumin at intervals	(2)
A. C.	65	♀	Right hemiplegia; cardiac hypertrophy	180-190	180/110	.....	.....	Negative	(3) - (4)
S. O.	70	♀	Carcinoma of left breast; metastases	160	160/ 90	4,310,000; hemoglobin, 70%	Urea nitrogen, 11.9; sugar, 123	Negative	(2)
S. S.	63	♀	Carcinoma of breast.....	160	100/ 65 124/ 80	3,650,000; hemoglobin, 65%	Urea nitrogen, 12; sugar, 96	Negative	(2)
H. J.	66	♂	Pseudobulbar palsy	Normal	102/ 68 202/102	.....	Urea nitrogen, 14.1; sugar, 150	Negative	(1); evidently a case of essential hypertension
A. K.	60	♂	General arteriosclerosis; cardiac hypertrophy; angina	200+	195/ 95 208/108	.....	Urea nitrogen, 19.7; sugar, 116	Trace of albumin	Glaucoma of right eye; atrophy of disk; retinal arteries; (5)
A. H.	45	♂	Left hemiplegia; general arteriosclerosis	200	180/104	.....	.....	Trace of albumin	(5)
A. G.	♂	45	Mitral stenosis and insufficiency; auricular fibrillation	Normal	May 7, 1926, 120/70; June 3, 1926, 208/110	.....	Urea nitrogen, 18.2; sugar, 117	Negative	Normal
M. E.	34	♂	Tabes	?	130/ 80	4,600,000; hemoglobin, 80%	.....	Negative	Optic atrophy which looked like partly simple and partly postneuritic; narrow blood vessels
D. P.	♂	37	Carcinoma of right breast; metastases to skeleton and cerebrum	160	150/ 90	3,200,000	.....	Negative	(2)
J. W.	47	♂	Chronic nephritis; arteriosclerosis; dilatation of aorta	190	196/120	.....	Urea nitrogen, 14.7; sugar, 118	Negative	(4)
A. K.	58	♂	Angina pectoris; hypertension	150	140/ 70 142/100	.....	Urea nitrogen, 9.8; sugar, 124	Negative	(1)
R. C.	40	♂	Neoplasm of left kidney.....	Normal	85/ 85	1,600,000; hemoglobin, 30%	Urea nitrogen. 9.1; sugar, 90	Negative	Optic atrophy; pale arteries; sclerosis of choroidal blood vessels
E. S.	64	♂	Mitral stenosis and insufficiency; aortic insufficiency; cardiac hypertension and dilatation; arrhythmia; chronic pulmonary emphysema	200	194/102	4,000,000; hemoglobin, 70%	Urea nitrogen, 18.7; sugar, 102	Albu[illegible]oderate trace, [illegible]ew granular c[illegible]	(4)
F. P.	56	♂	General arteriosclerosis; cardiac degeneration	200	154/100 190/108	3,940,000; hemoglobin, 76%	Urea nitrogen, 28.3; uric acid, 4.8 sugar, 103	Albumin, plus	(5)

I. G.	49	♂	Hypertension; right hemiplegia	180	170/100	.....	Urea nitrogen, 18.9; sugar, 104	Negative	(3); some arteries partially obliterated
D. P.	66	♂	General peripheral arteriosclerosis; atheroma of aorta; diabetes; gangrene of left foot	Normal	140/ 70 144/ 66	.....	Urea nitrogen, 13.3; sugar, 195	Albumin, plus; trace of sugar	(1); plus; case of nephritis rather than arteriosclerosis
S. S.	54	♂	Chronic nephritis; general arteriosclerosis	200+	216/138 200/134 230/140	5,100,000; hemoglobin, 80%	Urea nitrogen, 8.8; sugar, 103; cholesterol, 164	Albumin, plus; granular casts	(6)
F. S.	63	♂	Angina pectoris; coronary disease; endarteritis obliterans	170	160/ 92	4,576,000; hemoglobin, 80%	Urea nitrogen, 33.3; sugar, 107; cholesterol, 173	Dextrose, 3 plus	(3)
F. A.	60	♀	Hypertension; diabetes (?)...	Normal	165/ 78 204/ 84 180/ 70 150/ 68 Before attack of hypertension blood pressure subnormal for age, about 130	4,800,000; hemoglobin, 90%	Urea nitrogen, 15.5; sugar, 125	Specific gravity, 1.040; albumin, plus; trace of sugar; white blood cells and red blood cells; no casts	(1)
F. M.	65	♀	Diabetes mellitus; polyneuritis; hypertension; general arteriosclerosis	200	210/108 115/ 27 182/104	4,550,000; hemoglobin, 60%	Urea nitrogen, 14.7; sugar, 129	Negative	(6)
F. E.	45	♀	Diabetes mellitus	High	L, 130/ 78 R, 160/100 Before entering hospital, 210/100	5,600,000; hemoglobin, 95-100%	Urea nitrogen, 11.6; sugar, 142	Specific gravity, 1.029; slight trace of dextrose; red blood cells numerous	(4)
S. E.	70	♀	Diabetes mellitus; general arteriosclerosis; cardiac dilatation and hypertrophy	Normal	138/ 58	4,980,000; hemoglobin, 94%	Urea nitrogen, 12.5; sugar, 301	Specific gravity, 1.024; albumin, plus; sugar, 2 plus; white blood cells and red blood cells; finely granular casts	Diabetic retinitis; arteries normal in size, showed slight increase in reflex yet had exudates and hemorrhage; blood pressure should be normal
L. S.	62	♂	Left hemiplegia; general arteriosclerosis	200	240/130 230/130	3,600,000; hemoglobin, 70%	Urea nitrogen, 39.3; sugar, 138; creatinine, 2.5	Albumin, 2 plus, otherwise negative	(5)
A. F.	49	♂	Hypertension; emphysema; cardiac hypertension and dilatation; cardiac arrhythmia; angina	190	147/116 160/116	3,300,000; hemoglobin, 68%; Picture of pernicious anemia	Urea nitrogen, 20; sugar, 112	Albumin, 3 plus	(3); plus
H. S.	66	♀	Hypertension; chronic pulmonary edema; bronchitis; relative mitral insufficiency; general arteriosclerosis	190	178/106 210/100	4,180,000; hemoglobin, 80%	.....	Albumin, plus	(3) - (4)
L. S.	58	♀	Hypertension; moderate general arteriosclerosis; extrasystoles; angina; cardiac hypertrophy	200+	205/115	5,100,000; hemoglobin, 101%	Urea nitrogen, 13.2; sugar, 160	Albumin, 3 plus; sugar, plus; hyaline casts, plus; granular casts	Very narrow arteries and uneven in caliber
J. B.	66	♂	Hypertension; general arteriosclerosis; diabetes; cardiac arrhythmia	200+	215/118	4,500,000; hemoglobin, 82%	Urea nitrogen, 12.9; sugar, 170	Albumin, 4 plus; sugar, 2 plus	(5) (7); arterial walls in good condition but contracted in places
L. S.	55	♂	Cerebral neoplasm	Over 200	230/ 80	3,400,000; hemoglobin, 70%	Urea nitrogen, 17.4; sugar, 101	Negative	(7)

* In this column, ♂ indicates male; ♀, female.

atrophy of the retina and pigment epithelium. The choroid is clearly seen, and the choroidal blood vessels are light red or almost white and sharply outlined, giving the picture of a marked "tesselated" fundus. (Islands of choroidal pigment are clearly seen.)

There is another type of arteriosclerosis which might be called endarteritis obliterans, which is characterized by extremely narrow arteries, sometimes affected with perivasculitis, and accompanied by optic and retinal atrophy without the usual picture of tortuosities, exudates and hemorrhages. This type is associated with a blood pressure of over 200. Blocking of the central retinal artery or its branches may occur, usually, in the event of a temporary lowering of the blood pressure.

Such narrow arteries may sometimes be seen in retinitis pigmentosa, in which the blood pressure is not elevated.

High blood pressures are sometimes seen in patients who show hardly any sclerotic changes in the retinal arteries. In these cases the blood pressure is due to contraction of the arteries, and is marked by frequent variations in the degree of elevation. The urine is usually normal. The results of the chemical examination of the blood are apparently normal. Contracted arteries with irregular caliber, though of good color, may sometimes be seen in the fundus. This is generally known as essential hypertension. Patients may have transient cerebral attacks or intermittent claudication in the presence of high blood pressure; sometimes the blood pressure is normal. Contraction of the arteries may possibly be brought about by some change in the blood chemistry (such as increased cholesterol) or internal secretions or by the presence of bacterial toxins in the blood. The mechanism may be analogous to intermittent asthma. I have found a number of patients of this type in whose cases the diagnosis of hypertension with general arteriosclerosis was made. The appearance of the fundus put a different aspect on these cases. It has been proved that contraction of the arteries can occur. I can cite instances of such occurrence, which I observed during the entire process.

H. N., a young man, aged 23, came to my office complaining of attacks of blindness in the lower field of his right eye, which during three weeks previous to his visit recurred at intervals of three or four days. This blindness would last one or two minutes. His fundi were normal, and his retinal arteries were normal; his blood pressure was normal; he had an old mitral lesion. While I was explaining to him that these attacks were caused by a transitory disturbance of the circulation, the patient suddenly called my attention to the fact that he was just having one of these attacks. Taking him into the dark room without delay, I noticed that the upper branch of his retinal artery disappeared from view. While observing the fundus with the ophthalmoscope, I noticed a sudden rush of blood into the invisible artery. Simultaneously with the reappearance of the artery, the patient exclaimed that he could see again.

Recently, I saw a case in which there were similar attacks, that of a young woman, M. B., aged 23, who also had an old mitral lesion. For some reason, contraction was limited in this case to a branch of one retinal artery. A similar contraction of the coronary artery would cause angina. One does see cases of angina pectoris, without elevation of blood pressure, in which relief is obtained by nitroglycerin. It would be easy to understand that such contraction partially sustained in many places of the body, particularly in the kidney and other organs, would produce a functional hypertension.

Such contraction, if prolonged, could produce symptoms and damage caused by blocking of an artery. This would explain cerebral cases in which arteriosclerosis is not present. In actual arteriosclerosis, connective tissue replaces the unstriped muscle of the arterial wall, contraction gradually becomes less possible, and persistent high blood pressure is then brought about by the narrowing of the lumen of the arteries caused by sclerosis and hypertrophy of the heart.

Finally, I want to state definitely that in postmortem examination of the retinal arteries, the microscope does not disclose moderate changes, although such were recognized with the ophthalmoscope.

CONCLUSIONS

In going over the cases which I have compiled, the following conclusions may be drawn.

1. The height of the blood pressure is generally in proportion to the changes in the retinal arteries.

2. High nitrogen content of the blood is also usually in proportion to the changes in the retinal arteries. A high blood pressure seems to keep the urea nitrogen and kidney function normal in some cases.

3. In cases of advanced retinal arteriosclerosis, the urine is never normal; in incipient and moderate cases, it is frequently normal.

4. In the presence of normal retinal arteries a high blood pressure generally has a functional cause and is usually associated with a normal blood chemistry and kidney function.

5. In cases of auricular fibrillation, the blood pressure is frequently higher than one would expect from the appearance of the retinal arteries.

6. Patients with incipient and moderate arteriosclerosis without much elevation of blood pressure may suffer from hemiplegia or coronary disease with angina, probably caused by either contraction (spasm) of the arteries or thrombosis of a branch of an artery or vein.

7. Retinitis in the presence of good arteries is caused by toxemia or changes in the blood chemistry, such as is found in diabetes. It is not necessarily accompanied by elevation in blood pressure. It has no bear-

ing on prognosis, if the general condition is under control. Thromboses of veins give the fundus the spurious appearance of advanced arteriosclerosis, and careful inspection of the vessels of both eyes will give the examiner a clearer conception of the actual condition of the arteries.

8. Incipient changes in the retinal arteries are frequently unrecognized, even by many ophthalmologists, and reports on the condition of the fundus are often either misleading or insufficiently helpful.

9. Contractions of the arteries in normal and in incipient cases may be toxic in origin. In these cases, clinicians could concentrate on the removal of the cause and lowering of the blood pressure, without risk to the patient.

I wish to stress the importance of a close association of the internist and ophthalmologist, whose careful ophthalmoscopic report as an aid in diagnosis and prognosis should be taken more seriously than in the past.

SCLERODERMA AND CALCINOSIS *

ROBERT H. DURHAM, M.D.
DETROIT

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The subject of scleroderma has long been and continues to be one of pertinent interest, as evidenced by the vast amount of literature published on the subject during the past half century and even before. Similarly, the conditions resulting from disturbed or pathologic calcium metabolism have commanded increasing attention during recent years. The infrequent combination of these two interesting conditions, scleroderma and pathologic calcification, or calcinosis,[1] is the unusual clinical problem I wish to present.

The condition now termed scleroderma was not unknown to ancient medical men. Hippocrates, according to Bertolotti,[2] described in his "Traités des epidémies," the case of a certain Athenian whose skin was so indurated that it could not be pinched. Galen, in his "Traité de therapeutique," made note of a malady which he called "stegnose," described as a sort of obstruction of the pores of the skin with thickening, white spots, pigmentation and the absence of sweat glands. According to Arning,[3] in 1752, Curzio described a case of a peculiar

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1. Although the word calcinosis not infrequently appears in the medical literature, it is not found in medical dictionaries or in the new English dictionary. Its exact meaning is, therefore, undefined. Presumably it refers to local, multiple or generalized pathologic calcium deposits regardless of location. Its most frequent use has been with reference to such deposits in the skin and subcutaneous tissues.

2. Bertolotti, M. M.: Etude radiologique d'un cas de sclerodermie avec le syndrome de Profichet, Nouv. iconog. de la Salpêtrière **26**:291, 1913.

3. Arning, quoted by Kaposi, in Hebra: Diseases of the Skin, New Sydenham Society **3**:104, 1874.

induration of the skin under the title, "Dissertation anatomique et pratique sur une maladie de la peau d'une espece fort rare et fort singulière." But the honor of describing, in 1845 (*Gazette Médecine de Paris*), the first authentic case of scleroderma and introducing the title "Du sclereme chez les adultes" goes to Thirial. In 1854 Gillette [4] recapitulated twelve cases. Numerous other articles followed, and in 1894, Lewen and Heller [5] collected 507 cases. Innumerable articles have appeared since.

The first authentic report of calcinosis in association with scleroderma was described by a Swiss physician, Weber,[6] in 1878. Weber, however, interpreted the condition in his case as a form of gout. Although Lewen and Heller did not specifically differentiate cases in which calcareous depositions were present, a careful review of their monograph reveals descriptions which suggest that in six of their collected reports there was an associated calcification of the skin or subcutaneous tissues. A group of cases was not reported until 1911, when Thibierge and Weissenbach [7] described a patient who had combined scleroderma and sclerodactylia with calcinosis, and collected eight other cases from the literature. The literature has not been recapitulated since the date of their publication.

INCIDENCE OF SCLERODERMA

Scleroderma is not a rarity, and a few cases are seen each year in any large clinic. The 507 cases collected by Lewen and Heller apparently covered the interim from the publication of Thirial's article in 1845 to the date of their publication in 1895. I am reviewing the 645 reported cases of scleroderma in the medical literature from 1894 to 1926. The disease seems most prevalent in middle life, occurring most often between the ages of 20 and 40. Fifty-one cases of scleroderma neonatorum were found in this group. Many cases, however, occurred in elderly adults. Geographically, the disease is widely distributed. Of the 645 cases, 25 per cent occurred in France, 20 per cent in Germany, 16 per cent in England, 14 per cent in the United States, 7.5 per cent in Italy and 4.5 per cent in Russia. From the data at hand, it seems doubtful if the review of this large series of cases will contribute many new facts about the subject. The study is, however, affording an insight into the large variety of types, the unusual and sometimes bizarre

4. Gillette, quoted by Kaposi (footnote 3).

5. Lewen, G., and Heller, J.: Die Sclerodermie, Berlin, 1895.

6. Weber, H.: Cor.-Bl. f. schweiz. Aertze, 1878, p. 622.

7. Thibierge, G., and Weissenbach, A. J.: Concretions calcaries souscutanées et sclérodermie, Ann. de dermat. et syph. **2**:129, 1911.

associated conditions, and the divergent ideas as to etiology. The therapeutic agents described are many. It is interesting to record that spontaneous remissions were noted several times.

PATHOLOGIC PROCESS AND PATHOGENESIS OF SCLERODERMA

The pathologic process obviously is dependent on the type of the disease and its stage. Hypertrophy of the collagenous intercellular tissue is common to all types. The essential histologic changes consist of hypertrophy of the preexisting connective tissue bundles, followed by pressure on the vessels and epidermic structures. There is a considerable degree of perivascular and periglandular infiltration (lymphoid cells), and the papillae are at first swollen but later shrunken and flattened. The elastic tissue may be slightly increased in amount.

Innumerable theories have been advanced as to etiologic factors. After an analysis of 507 cases, including 28 autopsies, Lewen and Heller concluded that the pathologic process was dependent on an angioneurotic disturbance involving the peripheral as well as the central nervous system. A disturbance of various organs of internal secretion, particularly hypofunction of the thyroid gland, is a favorite theory. Recently, however, Marinesco and Goldstein,[8] in addition to collecting a number of cases with atrophy of the thyroid gland, found 26 cases associated with exophthalmic goiter. Others think that the cause is an increased tonus due to vasoconstrictor substances acting on the sympathetic nervous system. Touchard[9] believes it is an intermittent secretion of epinephrine. Kaposi,[10] Kobner,[11] Lassar,[12] Unna,[13] Nothhaft[14] and others feel that a change in the lymphatic glands due to protracted constriction produces hypertrophy of the collagenous tissues. Changes of the spinal cord have been described in autopsy reports in several instances. Vidal,[15] Crocker,[16] Bales,[17] and Newman[18] think that it is

8. Marinesco, G., and Goldstein, M.: Syndrome de Basedow et sclérodermie, Nouv. iconog. de la Salpêtrière **26**:*272*, 1913.

9. Touchard, quoted by Ravogli, A.: A Rare Form of Scleroderma, J. Cutan. & Genito-Urin. Dis. **35**:1, 1917.

10. Kaposi in Hebra: Diseases of the Skin, New Sydenham Society **3**:104, 1874.

11. Kobner, quoted by Ravogli (footnote 9).

12. Lassar, quoted by Ravogli (footnote 9).

13. Unna: Die Histopathologie der Hautkrankheiten, Berlin, 1894.

14. Nothhaft, quoted by Ravogli (footnote 9).

15. Vidal, quoted by Ravogli (footnote 9).

16. Crocker: Diseases of the Skin, Philadelphia, 1908, p. 618.

17. Bales, quoted by Ravogli (footnote 9).

18. Newman, quoted by Luithlen in a Mracek: Handbuch der Hautkreenkheiten, 1904, vol. 3.

a condition of the blood vessels. Dinkler [19] and Gaucher [20] also feel that it is a condition of the small arteries of the skin. Brown and O'Leary [21] studied the capillaries in five cases of scleroderma with a view of determining whether or not the finer vascular changes noted might be an etiologic cause. They concluded that the capillary deficiency and alteration peculiar to this disease did not precede the pathologic hypertrophy of the connective tissue bundles. Certainly there is not as yet enough uniformity of opinion to permit the acceptance of any single pathogenic factor as a cause of scleroderma.

INCIDENCE OF CALCINOSIS

Pathologic deposits of calcium in tissues have been reported in almost every portion of the anatomy; in muscle tendon, pericardium, myocardium, pleura, prepuce, scalp, eye and umbilicus, in all glands of internal secretion and in all the excretory organs. The incidence of local deposits in the skin is not frequent. It has been noted in a variety of conditions as follows: as calcium metastases in the skin, following local injury, in caseous tuberculous nodules, in carcinomas of the skin or in metastatic ossifying sarcoma (Finnerud [22]), on the basis of chronic inflammatory processes (Sehrt [23] includes syphilis and chronic dermatoses in this group) and as calcification of minute fat lobules. These are the solitary or multiple, freely movable lesions found in the skin of the extensor surface of the legs of old persons.

Kuznitsky and Melchior [24] found calcareous deposits in the skin in a case of universal fat atrophy, atypical lipodystrophia progressiva.

In many cases, both the skin and subcutaneous tissues are involved. It is evident that a sharp grouping cannot be made, as subcutaneous deposits of calcium also occur in the following conditions: various forms of tumors, including lipomas, fibromas, sebaceous cysts, sebaceous adenomas, "benign epitheliomas" and cystic adenomas connected with the sweat apparatus; subcutaneous veins and arteries (subcutaneous phleboliths); subcutaneous inflammatory nodules or scars; subcutaneous

19. Dinkler, Max: Zur Lehre von der Sclerodermie, Heidelberg, 1891.

20. Gaucher, Phillippe Charles E.: Maladies de la peau, Paris, 1909.

21. Brown, G. E., and O'Leary, P. A.: Skin Capillaries in Scleroderma, Arch. Int. Med. **36**:73 (July) 1925.

22. Finnerud, C. W.: Ossifying Sarcoma of the Skin Metastatic from Ossifying Sarcoma of the Humerus, Arch. Dermat. & Syph. **10**:56 (July) 1924.

23. Sehrt, E.: Ueber Knochenbildung in der Haut, Virchows Arch. f. path. Anat. **200**:395, 1910.

24. Kuznitsky, E., and Melchior, E.: Subcutane Lymphsackbildung und Kalkablagerungen in der Haut bei universellena Fettschwind, Arch. f. Dermat. u. Syph. **123**:133, 1916.

cysticerci; subcutaneous calcification in traumatic fat necrosis as in tissue in the breast, well described by Lecene and Moulonquet,[25] also by Lee and Adair.[26]

Riehl[27] noted deposits of calcium in the subcutaneous tissues in a case of leukemia.

Calcinosis of Skin and Subcutaneous Tissues.—Several such cases appear in the French and Italian literature under the title of "Profichet's syndrome".[28] Rather extensive calcinosis of the skin and subcutaneous tissues may appear without any apparent primary disease. Lhermitte[29] records a case of generalized subcutaneous calcification of unknown etiology. Morse[30] describes a case of extensive calcification of the skin and subcutaneous tissues in a child, aged 3½ years, occurring in areas of fat necrosis. The lesions had been present one year. The calcification was present at the borders of both axillae, at the left elbow, over the upper inner part of the thigh and buttocks, in the popliteal spaces and in the calves of both legs. There was no evidence of infection. Microscopic examination showed areas of degeneration of fat cells without cellular reaction. Morse's interpretation of the process was "a primary degeneration of fat followed by calcification and repair by avascular organization without giant cell formation. Lime seemed to deposit in the homogeneous hyaline material."[31]

This case of Morse's and the cases of calcification following traumatic fat necrosis described by Lecene and Moulonquet, and by Lee and Adair, seem to favor the hypothesis advanced by Klotz,[32] in discussing the origin of calcification from calcium soaps. He believes that the calcium is first laid down as soaps, later changing into the less soluble carbonate and phosphate.

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25. Lecene, P., and Moulonquet, P.: La cystosteatonecrose ou saponification intracellulaire du tissue cellulo-adipeux sous-cutané, Ann. d'anat. path. **2**:193, 1925.

26. Lee, B. J., and Adair, F. E.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **80**:670, 1924.

27. Riehl: Proc. 17th Intern. Cong. Med., 1913, section 13, pp. 179 and 188.

28. Profichet, G. C.: Sur une variété de concretions phosphatiques sous-cutanées (pierres de la peau), Thesis, Paris, 1900.

29. Lhermitte, J.: La calcinose généralisée et ses formes anatomiques interstitielle et sous-cutanée, Semaine méd. **30**:553, 1910.

30. Morse, J. L.: Calcification of the Skin in a Child, Am. J. Dis. Child. **22**:412 (Oct.) 1921.

31. It is of interest to note that Bernhein-Karrer (ueber Subkutane Fettgenebanekrosen beim Neugeborenen [Sog. Skelerodermie der neugeborenen], Schweiz. med. Wchnschr. **52**:12, 1922) describes a case of subcutaneous fat necrosis without calcification occurring in association with scleroderma neonatorum.

32. Klotz, O.: Studies upon Calcareous Degeneration: I. The Process of Pathological Calcification, J. Exper. Med. **7**:633, 1905.

Weidman and Schaffer [33] have recently described a case of calcification of the skin, including the epiderm, with extensive bone resorption. The patient was an elderly man. The sections of the skin that were studied were taken from the hand; this is apparently the first case described showing calcification of the epithelial structures and peripheral nerves. Since the serum calcium was normal, these authors feel that their case also supports the theory of Klotz, that "in the process of calcification there is a preliminary fatty metamorphosis of tissue and the final calcification comes about through a series of intermediate changes in which soaps figure."

"Calcinosis universalis" is a title applied by Verse [34] in referring to several cases of generalized deposits. He calls attention to the early changes in the intercellular substance of the connective tissue. Tilp [35] and von Gaza [36] have each reported a case of diffuse or universal calcinosis of unknown etiology.

Karvonen,[37] Reines,[38] and Liesegang [39] each describes cases of cutaneous calcification. Other cases of subcutaneous calcification are reported each by Ruggles,[40] Mauclaire [41] and Lesseliers.[42]

True bone formation may occur in the skin, in subcutaneous tissue or in scars. A case of calcinosis of the skin, which had progressed to osteoid tissue, has been described by Becker,[43] under the title, "Osteosis Cutis." He believes that the calcium deposition is but a preliminary step in the bone formation. Quoting Sehrt, Becker says "we are dealing

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33. Weidman, F. D., and Shaffer, L. W.: Calcification of Skin Including Epiderm in Connection with Extensive Bone Resorption, Arch. Dermat. & Syph. **14**:503 (Nov.) 1926.

34. Verse, M.: Ueber calcinosis universalis, Beitr. z. path. Anat. u. z. allg. Pathol. **53**:212, 1912.

35. Tilp, A.: Demonstration eines Falles von ausgebreiteter Kalzinosis, Verhandl. d. deutsch. path. Gesellsch., 1910, pp. 277-279.

36. Von Gaza: Ueber Calcinosis interstitialis universalis, Fortschr. a. d. Geb. d. Röntgenstrahlen **19**:372, 1912.

37. Karvonen, J. J.: Thokivista (Cutaneous Calculi), Duodecim, Helsing. **19**:319, 1903.

38. Reines, S.: Petrificatio cutis circumscripta, Arch. f. Dermat. u. Syph. **88**: 267, 1907.

39. Liesegang, R. E.: Ueber Kalkablagerungen der Haut, Arch. f. Dermat. u. Syph. **139**:73, 1922.

40. Ruggles, H. E.: Calcified Deposits in the Soft Tissues of the Left Forearm, Am. Atlas Stereo-roentgenol. **1**:82, 1916.

41. Mauclaire: Calcul sous-cutane de la face posterieure de l'avant-bras, Bull. et mém. Soc. anat. de Paris **94**:488, 1924.

42. Lesseliers, E.: A propos d'un cas de concretions calcarires sous-cutanes, Bull. Soc. de méd. de Gand. **75**:7, 1908.

43. Becker, S. W.: Osteosis Cutis, Arch. Dermat. & Syph. **10**:163 (Aug.) 1924.

with primary tissue death with secondary calcification and subsequent metaplastic bone production by the connective tissue." Breda [44] also reports a case with calcareous concretions which proceeded to bony tissue. Cases of true bone formation probably occur, however, without evidence of previous calcification. Various theories have been tendered to explain this type. One is the metaplasia of connective tissue into osteoid tissue, with the formation of true bony trabeculae if lime salts are deposited. In brief, as summarized by Wells,[45] pathologic calcification occurs in tissues that have suffered partial or total loss of vitality, or that have undergone hyaline degeneration; whereas in ossification, the accumulation of lime salts is within the stroma or cells of tissue which have changed to a homogeneous ground substance, with vitality decreased but not lost. In the latter, there is diffuse, even permeation of the salts in the tissue; in calcification, the deposits of lime salts remain in clumps or fuse into masses. Any type of cell or tissue sufficiently degenerated may become calcified, and any area of calcification may then be replaced by bone. Ossification occurs only in varieties of connective tissue. Deposits of calcium salt anywhere can stimulate connective tissue to form bone, although in the absence of calcium salts, cells normally osteogenic will not form bone. Moschcowitz [46] emphasizes that ossification without preliminary calcification is not found. The vascular supply must also be a factor in the process of ossification, a probable reason why calcareous concretions within hollow organs such as the appendix never reveal bone formation.

Calcinosis About Joints.—These cases are mentioned because they frequently occur in association with cutaneous or subcutaneous calcification, but a number of cases are reported in which the localization was around joints alone. The author has recently had five patients with deposits of calcium just outside the subdeltoid bursa. This condition is seen infrequently and probably differs in many respects from the cases with deposits in the soft parts near the joints of the phalanges or wrists. The latter type varies from fine deposits, called by French writers [47] "bony sand," to extreme calcification in soft tissues manifested as large visible tumors. Such a case of marked localized deposits has been observed by Hamlin,[48] who will publish it in detail. His patient, a

44. Breda, A.: Concrezioni calcari e produzioni steiformi nel connettivo sottocutaneo dell'uomo, Gior. ital. d. mal. ven. **50**:244, 1915.

45. Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

46. Moschcowitz, E.: Various Forms of Calcification and Ossification, Proc. New York Path. Soc. **13**:19, 1913.

47. Quoted by Delherm, Morel-Kahn, and Couput: Bull. et mém. Soc. d. radiol. méd. de Paris **13**:110, 1925.

48. Hamlin, L. E.: Personal communication.

young man, aged 23, had symptoms which began two years before observation and followed a local infection in the hand, caused by removal of a sliver with a jack-knife. Subsequently, small calcified nodules appeared around the phalangeal joints and throughout the soft tissues of the right metacarpus. These tumors have continued to increase in size and number. Two of the phalangeal joints became fluctuant, and many small calcareous nodules were discharged through a chronic sinus. X-ray examination showed heavy deposits of calcium salts, occurring as a fusion of innumerable small dotted areas scattered throughout the soft parts of the entire hand. There was particular localization around the phalangeal and metacarpal joints. The tendons or the tendon sheaths of the lower forearm also showed moderate calcification. X-ray examination of the remainder of the body did not show any other deposits or rarefaction of the bones.

Wildbolz [49] observed a case in which numerous nodules appeared around the joints of the hands and feet and later at the olecranon. The patient was a woman, aged 57, and the nodules had been enlarging and becoming more painful for six or seven years. Chemical examination of the concretion showed calcium carbonate, calcium phosphate and traces of magnesium. Uric acid and oxalic acid were absent. Microscopic examination showed the presence of leukocytes and giant cells, indicating an inflammatory process.

Ducasse [50] describes a similar case in a woman, aged 50. The concretions varied from 2 mm. to 3.5 cm. in diameter and were numerous over the extensor surfaces of the knees, elbows and fingers. Calcified concretions were also present in the main stem branches of the bronchi on the right side. The patient had previously expectorated concretions. Chemical analyses of the extruded deposits showed the presence of cholesterol and lime. Ducasse calls attention to the high cholesterol content in the blood in this case, 270 mg. per hundred cubic centimeters.

Wilens and Derby [51] report a case of multiple subcutaneous nodules of calcium in a boy, aged 5 years, occurring about the knee joints, in Scarpa's triangle, on the buttocks, the extremities and around the shoulder joints. The bulk of the deposits of calcium was in the fat and fibrous tissue of the subcutaneous layer. Fat necrosis did not occur as in Morse's patient.

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49. Wildbolz, H.: Ueber Bildung von phosphorsauren und kohlensauren Konkrementen in Haut und Unterhautgewebe, Arch. f. Dermat. u. Syph. **70**:435, 1904.

50. Ducasse, R. R.: Calcification of the Skin with Unusual Findings, Arch. Dermat. & Syph. **7**:373 (March) 1923.

51. Wilens, G., and Derby, J.: Calcification of Subcutaneous Tissue in Child (Calcinosis Universalis), Am. J. Dis. Child. **31**:34 (Jan.) 1926.

Tisdall and Erb [52] found extensive calcareous deposits over the epiphyses at both ends of the humeri, the proximal ends of the radii, ulnae and tibiae, and the distal ends of the femora, occurring in an infant 5 weeks of age.

Another condition of disturbed calcium metabolism, now a recognized entity and differing entirely from the foregoing types, is the so-called metastatic calcification of Virchow, studied and described by Wells,[53] Schulze [54] and others. In these cases there is an over-saturation of the blood with calcium salts, and deposits may occur without tissue degeneration. Wells points out that the deposits occur where the carbon dioxide is least abundant. To date, he has been able to collect only thirty-two cases from all the literature. The case described by Weidman and Shaffer [33] showed bone resorption, although the serum calcium was normal. Cases of demobilization of calcium from skeletal bones without deposition in the superficial tissues are reported as occurring in sepsis. In the new light of studies of the parathyroid hormone, it is likely that this type of case is a result of disturbed parathyroid function. Certain cases in which the condtion was regarded as metastatic calcification have been definitely associated with pathologic processes of the parathyroid glands. Thomas [55] reports a case of metastatic calcification in a boy in whom the two parathyroid glands were hypertrophied and measured 2 cm. in diameter. There was marked calcification in the small arteries, a large calcareous plaque in the skin of the right buttock and rarefaction of the long bones. Hubbard and Wentworth [56] report hypertrophy of the parathyroid glands in a case of metastatic calcification associated with chronic nephritis. Harbitz [57] feels that nephritis may at times lead to enough calcium retention to account for metastatic calcification. Normally, however, the serum calcium content of the blood is reduced in nephritis.

THEORIES AS TO PATHOGENESIS OF CALCINOSIS

It seems generally agreed that inflammatory changes are not a constant factor in calcinosis; yet many cases seem definitely to have followed

52. Tisdall, F. F., and Erb, T. H.: Report of Two Cases with Unusual Calcareous Deposits, Am. J. Dis. Child. **27**:28 (Jan.) 1924.

53. Wells, H. G.: Metastatic Calcification, Arch. Int. Med. **14**:574, 1915; Tr. Chicago Path. Soc. **9**:208, 1914-1915.

54. Schulze, F.: Skelettveränderungen als Ursache von Verkalkungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:243, 1923.

55. Thomas, W. S., in discussion on Weidman and Shaffer: Arch. Dermat. & Syph. **14**:503 (Nov.) 1926.

56. Hubbard, R. S., and Wentworth, J. A.: A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroid, Proc. Soc. Exper. Biol. & Med. **18**:307, 1920-1921.

57. Harbitz, quoted by Wells, H. G. (footnote 45, p. 443).

local inflammatory conditions. In the earlier stages, round and giant cells are seen infrequently; later, the concretions may act as a foreign body and produce some irritation.

Many observers have held that the deposits occur in or around degenerated tissue cells. Jadassohn [58] did not find any degeneration of the elastic or connective tissue fibers at the site of recent deposits. He feels, however, that the elastic fibers must be degenerated, though molecular and unrecognizable. Pospelow [59] mentions the affinity between elastic fibers and calcium salts and feels that deposits can probably occur in normal elastic tissue.[60]

Wildbolz,[49] Licharoff [61] and Lewandowsky [62] all concur that the calcification is a disturbance of inorganic metabolism, similar in character to gout, except that calcium salts are deposited instead of urates.

As to the mechanism of the calcium deposition, Pospelow feels that it is because the blood is saturated due to excessive amounts present, or because the solubility of calcium in plasma is changed, even though the amount of calcium in the blood has not risen above normal.

Hofmeister [63] found that as soon as a fluid in any way loses its free carbonic acid (as when the latter is bound to an alkaline medium), a deposition of calcium phosphate can occur under the condition and that the velocity of the fluid flow or a higher protein content does not hinder this deposition. Hofmeister also feels that the colloidal proteins play a rôle.

Tashiro [64] holds the view that the occurrence of insoluble calcium salts at one point must be intimately associated with a metabolism which forms bases. He states that calcification need not be preceded or accompanied by an abnormal amount of calcium in the blood; the essential thing is a local production of ammonia or other base forming compounds with a normal supply of calcium. Infection, mechanical irritation or changes in physiologic metabolism may be other factors.

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58. Jadassohn, J.: Ueber Kaltmetastasen in der Haut, Arch. f. Dermat. u. Syph. **100**:317, 1910.

59. Pospelow, W. A.: Ein Fall von Kalkablagerung in der Haut, Arch. f. Dermat. u. Syph. **140**:75, 1922.

60. Experimentally, Katase (Experimentelle Uerkalkung am Gesunden Tiere, Bietr. z. path Anat. u. z. allg. Path. **57**:516, 1913) injected calcium salts in animals and produced calcification in organs without previous injury to the cells.

61. Licharoff, quoted by Pospelow: Arch. f. Dermat. u. Syph. **111**:75, 1922.

62. Lewandowsky: Ueber subkutane und periartikulaire Verkalkungen, Virchows Arch. f. path. Anat. **181**:179, 1905.

63. Hofmeister: Experimentelles über Gewebsverkalkung, München. med. Wchnschr. **56**:1977, 1909.

64. Tashiro, S.: Studies on Alkaligenesis in Tissues: I. Ammonia Production in the Nerve Fiber During Excitation, Am. J. Physiol. **55**:519, 1922.

Oliver [65] pictures tissue calcification as a process similar to the formation of gallstones, the production of ammonia and the destruction of bile salts. Lichtwitz [66] mentions the possible part colloidal proteins may play in the induction of calcification. He thinks that precipitation of colloids in degenerated tissues may bring about a reduction in soluble crystalloids whereby the more insoluble salts such as calcium are precipitated. Hunter [67] concludes that calcification is a terminal phase of the fibrosis; that an alteration of the vitality of the sclerosed tissue determines the deposit of lime salts, analogous to deposits of calcium elewhere, as in sclerosed heart valves or in old tuberculous lesions.

Wells,[45] whose studies have been extensive, reviews the possibility that calcium is first bound as soaps. He was able to find only traces of calcium soaps in calcifying matter, and doubts if these soaps are an essential step in calcification, except in those cases in which areas of obvious fat necrosis are present. He feels that chemical precipitants in the tissue are not responsible, but that calcification depends on physicochemical factors and variations in the carbon dioxide concentration. He pictures calcification beginning as a simple physical adsorption by hyaline substance and dependent on the presence of a local alkalinity or perhaps a decreased amount of carbon dioxide in the fluids and tissues, and that calcification occurs whenever the proportion of calcium present in the blood is so great that it requires the effect of both the colloids and of the carbon dioxide in maximum concentration to keep it in solution.

In view of the number of divergent opinions reviewed, it is obvious that much confirmatory work remains to be done in order to establish universal agreement as to the applicability of one or more of these theories.

In summarizing, pathologic calcification occurs in almost all tissues of the body and at all ages. (Tisdall and Erb's [52] patient was 5 weeks of age, and Goldreich [68] reported a case occurring in an infant, aged 7 weeks.) In those cases in which the deposits occurred in the skin and subcutaneous tissues, the usual chemical composition is calcium phosphate and carbonate and traces of magnesium. Rarely, cholesterol may be present. Uric acid is not present. Generally speaking, inflammatory changes are not a factor. The deposits are believed to occur in or

65. Oliver, quoted by Ducasse, R. R.: Calcification of the Skin, Arch. Dermat. & Syph. **7**:373 (March) 1923.

66. Lichtwitz, L.: Ueber die bedeutung der Kolloide für die Konkrementbildung und die Verkalkung, Deutsche med. Wchnschr. **36**:704, 1910.

67. Hunter, W. K.: Sclerodermia with Subcutaneous Calcareous Deposits, Glasgow M. J. **79**:241, 1913.

68. Goldreich, A.: Ein 7 Wochen Alter Knabe mit Zellgewebsverhartung, Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien. **13**:57, 1924.

around degenerated tissue cells. Numerous observers say that the deposits do not occur in normal tissues. In instances in which this appears to be the case, the theory is offered that toxins have lowered the vitality of the cells.

REVIEW OF CASES FROM THE LITERATURE

Scleroderma and calcinosis occur together most infrequently. It seems safe to say that less than a dozen cases had been reported prior to 1911. With a more prolific medical literature, a larger number of cases has since appeared.

In 1913, Bertolotti [2] observed and described in detail the clinical and roentgenographic study in a case of scleroderma accompanied by well marked acrocyanosis and sclerodactylia. The patient was a woman, aged 36, whose symptoms began at the age of 30. The scleroderma was maximum in the extremities. There were distinct bands about the elbows, knees and feet, in areas of which were scattered small indurated nodules of calcification. Similar concretions were also present in the soft tissues of the terminal phalanges and along the forearm in an area of scleroderma. Localized muscular atrophy resembling an interstitial myositis was also present. Most of the larger tendons were retracted, indurated and calcified. There was localized osseous atrophy in the terminal phalanges, symmetrical on the two sides. Comparative x-ray studies after a year's interval evidenced progressive resorption of the phalangeal bones. A chemical analysis of the concretions mixed within the horny layer showed the presence of calcium salts. There was a disturbance of internal secretions with atrophy of the thyroid gland and other signs of hypothyroidism, as well as roentgenographic evidence of hypophyseal hypertrophy. Although Bertolotti was unable to prove which process was primary, he believed that the condition resulting from the scleroderma favored the deposition of the calcium. He also cited other instances in which calcification had followed trophic and degenerative disturbances. The rather rapidly developing bony changes suggest that this is a case of metastatic calcification with scleroderma.

In 1913, Hunter [67] also reported a case of scleroderma with subcutaneous calcareous deposits associated with Raynaud's disease. The patient, a woman, aged 38, had suffered from symptoms referable to Raynaud's phenomena since 14 years of age. The scleroderma had been present since the age of 18, and subcutaneous concretions first appeared at the age of 21. The scleroderma involved the skin of both hands, lower arms, face, neck, back and buttocks. The calcified deposits were much more limited and were present around the joints of the fingers especially, and had been extruded from the skin around the metatarsophalangeal joints and from the region of the left elbow. Chemical

studies of the deposits showed the presence of carbonate and phosphate of calcium and magnesium. Uric acid was absent.

Previous reports of cases had been made in England or continental Europe. In 1917, Olson [69] described the case of a young woman, aged 27, who had sclerodactylia with sclerodermatous changes involving the palmar surfaces of the hands. Numerous small calcareous concretions were present in the tissues of the fingers and near the olecranon. They were composed largely of carbonates. Urates and uric acid were absent.

A case of calcification about an ulcerated area of scleroderma of the face is described by Pollitzer.[70] The patient was a man, aged 47, of German descent. The scleroderma (diagnosed by Kaposi, Vienna) began on each side of the face nineteen years previous to examination, but later underwent a remission with marked improvement. Scattered areas of scleroderma reappeared on both sides of the face when the patient was 32 years of age; numerous ulcerations appeared with calcified plaques projecting through the ulcers and involving extensive areas of surrounding subcutaneous tissues. Chemical examination of the concretions was not recorded.

A case of scleroderma with small pleomorphic calcareous deposits occurring in a boy, aged 4, was reported by Langmead.[71] The patient had an amentia of the mongolian variety, but not as marked as the average case. Bluish discoloration of the skin had been noted since birth. At the age of 3, scleroderma began to appear over the upper part of the arms, shoulders and thighs, with hard subcutaneous nodules varying "from minute areas to the size of a shilling." X-ray examinations showed a marked infiltration of calcareous deposits in the subcutaneous tissues involved. Symptoms of the joints involving the knees and ankles were developing. Although the fingers were small and shiny, definite sclerodactylia had not appeared.

In 1923, Bayless [72] reported the case of a woman, aged 64, who had extensive scleroderma involving the hands, feet, chest and abdomen, with large and small calcified nodules projecting through the skin of the hands, wrist and great toes. Nodules could not be palpated through the skin of the chest or abdomen. The scleroderma had been progressing for a number of years; arthritic symptoms had been present for seven years; small calcified nodules appeared on the back of the wrists four

69. Olson, G. M.: Sclerodactylia with Calcareous Concretion, with Report of a Case, J. Cutan. Dis. incl. Syph. **35**: 96, 1917.

70. Pollitzer, S.: Ossification in a Case of Scleroderma, J. Cutan. Dis. incl. Syph. **36**:271, 1918.

71. Langmead, F. S.: Sclerodermia with Calcification in a Mongol, Proc. Roy. Soc. Med. **12**:94, 1918-1919, Sect. Dis. Child.

72. Bayless, B. W.: Scleroderma, Kentucky M. J. **22**:39, 1924; Radiology **6**: 239, 1923.

years before. X-ray examinations showed that these were unattached to the bone. An atropic arthritis of the phalangeal articulations was present. There was marked contraction over the tips of the fingers suggesting an accompanying sclerodactylia.

Tisdall and Erb [52] describe two unusual cases of calcification in children. One of their patients, a boy, aged 12, had extensive deposits of calcium in the subcutaneous tissues of both legs, arms and buttocks with generalized skin changes, the diagnosis of which rested between xeroderma pigmentosum and scleroderma. Biopsy and examination of a section of the skin containing a calcareous nodule resulted in a final diagnosis of scleroderma.

A case of scleroderma with sclerodactylia, accompanied by calcinosis or "calcium gout" was described by Merklen and Vallette [73] in 1924. The patient was a single woman, aged 55. Symptoms of scleroderma began to be manifested at the age of 42, coincident with her menopause. Two years later, well marked sclerodactylia had appeared, involving all the fingers. The scleroderma involved the hands, arms, face and neck. In the region of the left elbow and forearm, inflammatory areas appeared through which were extruded chalky concretions containing lime salts. Analyses did not show cholesterin or uric acid. Roentgenograms revealed the presence of numerous masses around the terminal phalanges and joints of fingers of both hands and around the elbow joint. In this case, the authors felt that the trophic disturbance of the skin preceded the appearance of the concretions. The calcification was found only in the areas of scleroderma.

Delherm, Morel-Kahn and Couput [74] describe briefly the roentgenographic observations in two cases of scleroderma. In one, there was an ankylosis of the phalangophalangeal joints with disappearance of the articular space; the metacarpophalangeal joints remained unchanged. In the second case, there were also articular lesions, involving the metacarpophalangeal interspace with osseous rarefaction, more accentuated at the distal ends of the phalanges. Near the end of the phalanx of the index finger was a group of small deposits of calcium, numbering seven or eight, similar to "bony sand," but described "as the deposits seen in the cutaneous cellular tissues in the course of scleroderma."

A case in which there were subcutaneous calcium nodules on the fingers of both hands and at the elbow with sclerodactylia was reported by Davis [75] in 1912. The patient, a woman, aged 34, had suffered from

73. Merklen, W. M., and Vallette, A.: Scleroderma avec concretions calcaires, Bull. Soc. franç. de dermat. et syph. **31**:120, 1924 (Reun. de Strasb.).

74. Delherm, Morel-Kahn and Coupout: Sclerodermie et lesions osseuses, Bull. et mém. Soc. de radiol. méd. de Paris **13**:110, 1925.

75. Davis, H.: Case of Raynaud's Disease Associated with Calcareous Degeneration, Proc. Roy. Soc. Med. **5**:99, 1911-1912; Dermat. Sect.

chilblains as long as she could remember and Raynaud's disease had been present for many years. The hard nodules first appeared eight years before while she was nursing her first baby. The nodules gradually worked their way through the skin and calcareous material was discharged for some time. Chemical examination showed the presence of calcium carbonate and phosphate.

In 1911, Scholefield and Weber [76] observed a similar case in an unmarried woman, aged 50. In childhood the patient began to have chilblains. At the age of 35, sclerodactylia was noted and progressed gradually. Subcutaneous concretions formed under the skin of the fingers and around the left olecranon. Extensive metabolic studies were not made. The concretions, however, did not contain urates.

Logan [77] reports a case of Raynaud's disease in a woman, aged 60, with numerous calcareous nodules on the lateral and flexor surfaces of all the digits. The patient had suffered from chilblains involving the hands, feet and ears as long as she could remember. Some of the lumps became acutely inflamed and ulcerated, extruding the deposits. Chemical studies showed the presence of phosphate and carbonate of lime; no trace of uric acid was present.

Symptoms and disorders of the joints frequently accompany scleroderma. In 1898, Dercum [78] noted and pointed out this frequent relationship. Claude, Rose and Bouchard [79] describe a case of scleroderma, sclerodactylia and chronic articular difficulty. Apert [80] has also reported a case of scleroderma with ankylosed joints in a child, aged 12 years. Other observers—Leontjewa,[81] and Adrian and Roederer [82]—also found arthropathies due to calcification accompanying scleroderma. More frequent x-ray studies would undoubtedly reveal a greater incidence of calcinosis about joints in cases of scleroderma.

Of interest, also, are two cases of scleroderma with subcutaneous fibrous nodules without calcification. The patient observed by Gray [83]

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76. Scholefield, R. E., and Weber, F. P.: A Case of Sclerodactylia with Subcutaneous Calcification, Brit. J. Dermat. **24**:200, 1912.

77. Logan, J. R.: Unusual Calcareous Deposits in the Soft Tissues of the Hands, Arch. Radiol. & Electroth. **28**:55, 1923-1924.

78. Dercum, F. X.: On Scleroderma and Chronic Rheumatoid Arthritis, J. Nerv. & Ment. Dis. **25**:703, 1898.

79. Claude, Rose and Bouchard, quoted by Bertolotti (footnote 2).

80. Apert, E.: Sclerodermie avec arthropathies ankylosantes et atrophie musculaire chez une enfant de douze ans, Bull. Soc. franç. de dermat. et syph. **19**:244, 1908.

81. Leontjewa, L. A.: Ueber veränderungen der Knochen und Gelenke bei Skerodermie, Arch. f. klin. Chir. **128**:293, 1924.

82. Adrian, C., and Roederer, J.: Les arthropathies au cours de la sclerodermie, Ann. de dermat. et syph. **1**:299, 341 and 395, 1920.

83. Gray, A. M. H.: Generalized Sclerodermia with Subcutaneous Nodules, Proc. Roy. Soc. Med. **16**:107, 1922-1923; Sect. Dermat.

had generalized scleroderma with innumerable subcutaneous nodules attached to tendon sheaths, capsules of joints and periosteum and on the backs of the hands and feet. Microscopic examination showed the presence of fibrous tissue that had undergone hyaline degeneration. It is interesting to speculate as to whether these hyaline changes were a forerunner of calcification. Bruhns [84] also describes a case of nodular tumors of the skin which were present over the abdomen, scapular region and left axilla. Typical scleroderma "en bande" was also present.

I shall add to the previous nine cases of scleroderma and calcinosis collected and reported by Thiberge and Wiessenbach, and to the foregoing thirteen cases reviewed (including three cases of sclerodactylia with calcinosis) the report of the case of another patient who came under my own observation.

AUTHOR'S CASE [85]

A white woman, aged 67, about thirty-seven years before examination had an ulcer appear on the lower portion of the right leg; edema of both legs was marked at times, and small bonelike areas appeared in the cutaneous tissues, gradually becoming more numerous. The ulcers finally healed, but recurred at intervals. Active ulceration had been present on both legs for seven years. The skin over the lower part of the legs became tight and drawn. The small dots of bonelike deposits gradually became more numerous and fused into large plaques in and around the ulcerated areas. There was nothing to suggest the presence of syphilis or tuberculosis in either the personal or the family history. Varicose veins were not present. Small areas of calcification in patches of scleroderma were also present over the forehead. The skin of the fingers was tight and drawn. The lower third of both legs was pigmented, dark brown and scarred, and the skin was tight. Innumerable small calcified areas could be palpated just beneath the surface, and in many places they protruded through the skin, becoming fused into irregular plaques. X-ray examinations showed extensive subcutaneous calcified deposits in the lower half of both legs, and calcified nodules around numerous joints. The patient had advanced chronic nephritis and died from uremia. The serum calcium was 7.4 mg.

A postmortem examination showed extensive calcification through the entire vascular system. Several of the large arteries and veins had the form of a solid tube. A large calcified mass was present in the myocardium. The right saphenous vein was replaced by a solid chain of calcified nodules. Three parathyroid glands were present, and were of ordinary size. The histologic structure seemed essentially normal.

The gross anatomic diagnoses were: generalized arteriosclerosis with extensive calcification; atheromatous ulcers, thrombus formation and aneurysmal dilatation of the aorta; phlebosclerosis; calcification of the mitral valve and adjacent myocardium; mitral insufficiency and slight stenosis; cardiac hypertrophy; sclero-

84. Bruhns, C.: Ueber Knotenbildungen bei Sklerodermie, Arch. f. Dermat. u. Syph. **129**:178, 1921.

85. This case has been reported in detail (Durham, R. H.: A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, Ann. Clin. Med. **5**:679 [Jan.] 1927).

derma of the legs, hands and forehead; subcutaneous calcified nodules and plaques in the regions of the legs and elbow; ulcers of the legs, with pigmentation and old scars; limitation of motion of the knee joint; edema of the ankles; chronic nephritis (small granular kidney); acute purulent bronchitis; early lobular pneumonia; hyperplasia of the tracheobronchial and cervical lymph nodes; old scars of the apexes of the lungs; calcification of the bronchial lymph nodes; colloid adenomas and old scars of the thyroid gland; duodenal ulcer; cholelithiasis; localized hyaline thickenings of the splenic capsule and senility.

TABLE 1.—*Chemical Determinations of the Blood*

	Blood Serum Calcium	Calcium Whole Blood	Inorganic Phosphorus	Phosphorus	Carbon Dioxide	Cholesterol	Fatty Acids	Sugar	Nonprotein Nitrogen	Uric Acid	Urea Nitrogen
Observations in Scleroderma and Calcinosis											
Tisdall and Erb [52]	9.7	...	4.4	...	..	...	...	...	....	....	....
Merklen and Vallette [73]	...	...	...	7.7	..	107	...	...	....	2.3	4.2
Gitlow and Steiner: Arch Derm. & Syph. 9:549, 1924	7.2 6.31	...	...	...	50	223	...	70	33.7	4.7	11.25
Bayliss [72]	...	...	...	7.5	..	...	...	123	....	4.02	7.2 7.2
Durham [55]	7.6	...	4.77	...	..	...	...	89	37 60	3.96	17.3
Comparative Observations in Calcification without Scleroderma											
Calcium about joints in infant (Tisdall and Erb [52])	9.3	...	4.5	...	..	...	...	...	....	....	....
Calcium about joints (Ducasse [50]-Tucker)	...	10.22	...	N*	..	270	...	N	N	....	....
Calcium following local infection (Pospelow [59])	10.45	...	...	...	..	...	...	...	....	....	....
Epidermal calcification (Weidman and Shaffer [63])	9.1 11.8	...	...	...	..	188	300	89	....	3 6	16
Subcutaneous calcification (Wilens and Derby)	...	N	N	...	..	...	...	...	....	....	....
Metastatic calcification (Wells [45])	†	†	...	...	..	...	...	...	....	....	....

* "N" refers to a reported normal reading.
† No figures available; thought to be increased (Wells, H. G., personal communication).

LABORATORY OBSERVATIONS

Composition of Concretions.—The concretions spontaneously extruded or excised from the cutaneous tissues have uniformly shown the presence of calcium phosphate and carbonate. Hunter,[67] Wildbolz [49] and others recorded the presence of small amounts of magnesium also. Uric acid and urates have always been absent, showing that the process is not related chemically to gout. Quantitative determinations were not recorded. Wells, however, found that the composition of most pathologic deposits of calcium salts in the calcified areas in the body seems to be practically the same if not identical, whether laid down normally

(ossification) or under pathologic conditions. His analyses showed that the $CaCo^3$ varied from 10 to 15 per cent, and the $Ca^3(PO_4)^2$ from 85 to 90 per cent.

Chemical Examinations of the Blood.—In studying the chemical analysis of the blood in skin diseases, Pulay [86] found the calcium content high in two cases of scleroderma. Gitlow and Steiner obtained low figures for the serum calcium in one case observed. It is evident from table 1 that there is considerable variation in the serum calcium, even in the same type of case. The figures are important mainly in showing that there is not constant oversaturation of the blood with the calcium salts in scleroderma, as there is supposed to be in metastatic calcification.

COMMENT

Although combined cases of scleroderma and calcinosis are rare, the number of reported instances is sufficient to suggest that there is such a clinical and pathologic entity. In Lewen and Heller's series there was an average of one case of the combined condition in every eighty-four cases of scleroderma reported. In my series, the average is one case of scleroderma and calcinosis to every sixty cases of scleroderma. It is true that it might be questioned whether these figures indicate more than a coincident relationship of the two conditions. On the other hand, it is doubtful that x-ray examinations have been made in any large percentage of cases of scleroderma. The close local relationship of the two conditions offers the strongest suggestion that they are not present by chance in the same person. In several cases of calcinosis with localized scleroderma, the deposits were present only in the areas of skin sclerosis. Furthermore, the deposits in the tissues of the phalanges, in cases of sclerodactylia and scleroderma involving the hands, seem fairly characteristic; although it is true that similar deposits, which followed local infections, are sometimes described without the accompanying skin condition. It seems logical to conclude that there is a definite relationship between the two processes despite the infrequent occurrence.

The priority of the appearance of the scleroderma or the calcinosis is not always made plain in the reported cases. Even though the changes in the skin are not recognized in the early stage, in those cases in which priority is mentioned, the sclerosis of the skin usually antedated the recognition of the calcified nodules.

Geographically, four cases are recorded to have occurred in England, three in France and six in the United States. Most cases of uncomplicated calcinosis are reported in the literature of France and Germany.

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86. Pulay, E.: Sklerodermie mit Sklerodaktylie, Wien. med. Wchnschr. **71**: 982, 1921.

Deductions cannot be drawn from the ages of the patients. Two cases occurred in boys, aged 4 and 12. The only man in the group was 47; the recorded ages of the four other patients, women, were 36, 27, 38 and 64, respectively. The three cases with sclerodactylia occurred in women, whose ages were 34, 56 and 60. It is noteworthy that the time of onset in practically all of the cases in adults was early adult or middle life.

The concretions varied from small dots in the soft tissues around phalangeal joints to extensive areas of bonelike plaques, numerous deposits having become fused. The calcinosis was not limited to any single type of scleroderma, but occurred in most of the forms: the symmetrical, the generalized, the circumscribed (morphea) and the digital. No case of morphea guttata (white spot disease) was mentioned. The sclerosis of the skin likewise varied from involvement of a portion of the hands to generalized, widespread, symmetrical lesions.

Pathologically, the combined process does not differ from that of scleroderma, with the addition of foreign bodies scattered through the superficial or connective tissues. The epidermis is thin, with relative thickening of the horny layer. The fibrous layer of the dermis is thickened, and subcutaneous cellular tissue is replaced by a dense connective tissue, more dense in the deeper parts. The deposits of calcium are found mostly in the midst of the dense connective tissues, but may be more superficial.

All of the cases were under current clinical observation. No case had come to autopsy except the one reported by me. There seemed to be slow but definite progress of both types of lesions, particularly in older persons. Except in my case, the condition had not been a factor in a fatality; this case had progressed for thirty-seven years.

As the etiologic factor of scleroderma is by no means agreed on, and since opinions as to the causative mechanism of pathologic calcification are at such wide variance, ideas concerning the combination of these two conditions are even more puzzling. As is true in uncomplicated calcinosis, the variety of types and anatomic relationships add to the difficulty in arriving at conclusions that universally apply to all cases. For example, the question arises whether the small pleomorphic deposits in the phalanges, as seen in both Raynaud's disease and scleroderma, have the same etiologic factor; also whether the basic factor in their deposition is similar to that in cases with subcutaneous, periarticular and vascular involvement, which is sometimes extensive. The question also arises as to the relation or origin of such deposits without scleroderma. The cases in which the deposits are small and dotted predominate, and their presence raises a number of hypotheses about an alteration of the local metabolism of the skin and subcutaneous tissues, the process being more pronounced in scleroderma.

There are several mechanisms through which calcification might conceivably occur in association with the scleroderma: (1) as a result of parathyroid dysfunction, (2) as metastatic calcification, (3) by simple chemical precipitation and (4) by means of a physicochemical disturbance in which colloidal proteins play a rôle.

In experimental calcification, such as Hueper [87] and others produced by injecting parathyroid hormone, the deposits occurred most frequently

TABLE 2.—*Recapitulation*

Sex	Age	Age at Onset	Location of Scleroderma	Location of Calcium Deposits	Accompanied by Sclerodactylia	Accompanied by Raynaud's Disease
			Cases of Scleroderma with Calcinosis *			
F	36	Scleroderma 30	Extremities, elbows, knees, feet	In areas of scleroderma, in terminal phalanges and in larger tendons	Yes	Yes
F	38	Scleroderma 18 Calcinosis 21	Hands, lower part of arms, face, neck, back and buttocks	Phalangeal, metatarsophalangeal and regions of left elbow	....	Yes Onset at 14
F	27	.....	Palmar surface of both hands	Phalanges and near olecranon	Yes	
M	47	Scleroderma 28	Both sides of face	In areas of scleroderma	No	Yes
M	4	3	Upper part of arms, shoulders and thighs	In area of scleroderma	?	Yes
F	64	57	Hands, feet, chest abdomen	In hands, olecranon and great toes	Yes	
M	12	?	Generalized	Both legs, arms and buttocks		
F	55	Scleroderma 42	Hands, arms, face and neck	Forearm, joints of both hands and left elbow	Yes	
F?	67	30	Legs and fingers	In areas of scleroderma, around many joints, widespread in cutaneous tissues	Yes	
			Cases of Sclerodactylia with Calcinosis			
F	34	Scleroderma 4 Calcinosis 26		Fingers of both hands and at elbow	....	Yes
F	50	Scleroderma 35		Fingers and around left olecranon		
F	60	Childhood		Lateral and flexor surface of all digits		

* Details of two cases of scleroderma with calcinosis (reported by Delherm, Morel and Couput) were not supplied.

in the excretory organs, the lungs, stomach and kidneys. The tissues of these organs are more alkaline because of their continuous excretion of acids. As the secretion from the sudoriparous glands is normally neutral or slightly alkaline, and since the interglandular tissues around the sweat glands are slightly acid after the alkaline secretion, the occurrence of deposits of calcium in the skin or subcutaneous tissues as a result of parathyroid disturbance does not parallel experimental observations. Histologically, too, there is a difference. In the experimental

87. Hueper, W.: Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

type, the deposits of calcium were found in the interglandular tissues around the excreting glands; whereas in the reported cases, with cutaneous and subcutaneous involvement, the deposits were not in the interglandular tissues, but were scattered diffusely throughout the connective tissue.

If parathyroid dysfunction is accompanied by histologic changes in the gland, such pathologic processes are rarely found. As before indicated, the parathyroid glands in my case seemed normal in histologic appearance.

An interesting corrollary, however, is some recent work showing that the secretions of the thyroid and the parathyroid glands exert an antagonistic effect on each other; at least, several investigators have found that animals tolerate much more thyroid extract when parathyroid hormone is administered simultaneously. Since thyroid dysfuncton is a frequent topic of discussion as a factor in scleroderma, and since parathyroid glands exert a regulatory influence on calcium metabolism, one might conjecture that there is a thyroid-parathyroid syndrome in the dual process.

The cases regarded as metastatic calcification present several essential differences from the collected cases of calcinosis with scleroderma. It is felt that the metastatic deposits may occur in tissues without demonstrable cell injury; whereas in the cases of scleroderma with cutaneous, subcutaneous or periarticular deposits, extensive vascular changes with alteration of the blood supply to the tissues and structural cell changes have been demonstrated. Rarefaction of skeletal bones is usually a constant occurrence in so-called metastatic calcification. In the cases of calcinosis with scleroderma there was no rarefaction, except osteoporosis resulting from disuse. In my case, the larger bones, particularly the calvaria, showed a marked increase in density. In none of the cases studied was there an oversaturation of the blood with calcium salts, as is thought to be a regular feature in the metastatic variety. The theory of metastatic calcification is incompatible, further, since this type of deposit is said to occur in places where the blood contains the least carbon dioxide. Obviously this condition is not present in the peripheral tissues. It seems unlikely, therefore, that the mechanism of calcification with scleroderma is similar to metastatic calcification.

Simple chemical precipitation of calcium salts occurs on the basis of alteration of the composition of the secretions, as is frequently seen in the cells and tubules of the kidney. As sweat contains a total of 0.57 per cent of inorganic salts, of which the alkali sulphates and phosphates comprise 0.18 per cent, and since the excretory function of the skin is definitely altered in scleroderma, the simplest conception would be that the normal excretory mechanism is sufficiently changed to cause calcium retention and local deposits.

Possible, but remaining to be proved, is the theory that as a result of sclerotic changes there is in or around the involved areas a local alteration of the normal p_H of the cells and tissue juices. With excretion diminished, these tissues would be expected to become more alkaline. It is known, too, that calcium salts are less soluble in an alkaline than in an acid medium; hence, precipitation might occur on the basis of a decrease of the solubility of the calcium salts in the tissue fluids or as a result of decreased solubility in the blood which flows through these altered areas. Obviously, these explanations do not throw any light on the numerous instances of deposits found in deeper tissues and around large and small joints not in areas of scleroderma. The frequent occurrence of cutaneous and subcutaneous deposits within sclerotic skin areas must, however, be of some significance.

Several observations have been made to determine whether the marked alteration of morphology and function of capillaries occurring in scleroderma would aid in determining what local chemical or metabolic disturbances result. Brown and O'Leary [21] studied five so-called true cases of scleroderma, and found a quantitative deficiency of the capillary loops which roughly paralleled the trophic changes; they also observed many huge loops of increased length. Vasomotor phenomena were slight or absent. In five cases of the vasomotor type (Raynaud's disease with sclerodermatous changes), dilatation, stasis and disturbances of permeability were evident, to a great extent resembling the picture seen in true Raynaud's disease as described by Brown.[88] The disturbances of the skin were apparently secondary to the abnormal vasomotor reactions. Gitlow and Steiner also noted enlargement of capillaries and sluggish flow of blood. The venous ends were distended like bulbs. I have made similar observations. In a case of scleroderma involving the hands and arms, normal capillary function was first studied; subsequent studies were made after hypodermic injection of 2, 3 or 4 minims (0.123, 0.184 or 0.246 cc.) of epinephrine. Even 2 minims of this drug produced almost complete stasis in small capillaries, with pronounced slowing of the blood flow in the larger ones. The effect was fairly prolonged. The impression was gained from this one case that the effect of epinephrine seemed much more marked in the capillaries than was observed in normal controls. More careful subsequent studies are being planned with loop counts, diameter observations and records of the blood pressure. Should this observation be substantiated in other cases, the theory of endocrine influence as a factor in scleroderma may be strengthened further.

88. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med. **35**:56 (Jan.) 1925.

These observations on the peripheral circulatory sluggishness seem most important, however, in connection with Hofmeister's [63] chemical observations previously quoted. It is his belief that as soon as a fluid in any way loses its free carbonic acid (for example, when the latter is bound to an alkaline medium), provided there is no increase in the velocity in the fluid flow or a higher protein content, a deposition of calcium phosphate can occur. These two observations do not permit final deductions, but may add a link in the chain of evidence.

Another likely possibility is that the colloidal proteins play a prominent rôle. Wells feels that the carbon dioxide in maximum concentration plus the effect of the colloids ordinarily prevents calcium deposition, unless the content of the blood calcium is much higher than normal. Hueper feels that the albuminous substances and the phosphates of the blood normally keep the calcium salts in solution and buffer greater changes in the p_H of the blood, thereby preventing precipitation of the calcium. He advances the hypothesis that a decrease in the amount of albuminous substances in the blood, as is found during nephritis (when considerable quantities of the blood albumin are excreted through the kidneys), offers a mechanism for the precipitation of calcium salts. Although such an explanation might fit in with the unusual degree of subcutaneous, vascular and periarticular calcinosis found in my case, in many other cases a history of heavy excretion of albumin or marked renal pathologic change was not emphasized. A further consideration is that the solubility of the calcium in the plasma is changed, although the amount of calcium in the whole blood is not above normal.

Thibierge and Weissenbach, after a detailed study of their case of scleroderma with sclerodactylia and calcinosis, felt that the elastic fibers did not play any part in the calcification, which they considered secondary to the formation of a more or less dense connective tissue, parts of which underwent a sort of colloid degeneration which favored the deposition of lime salts. This uncomplicated explanation, also favored by Jadassohn, may possibly be the most important factor in the process. No theory yet advanced, however, is sufficient in any way to explain why scleroderma and calcinosis are so infrequently associated. The lack of detailed histologic and biochemical information about the individual cases prevents more than speculative deductions. A further correlation of accumulated data by physiologists and physiologic chemists may aid in an explanation of the problem.

SUMMARY

1. Fourteen cases of calcinosis associated with scleroderma or sclerodactylia have been collected and added to the nine cases reported in 1911.

2. In four of the eight cases of scleroderma and calcinosis, there was an accompanying sclerodactylia. In three cases of sclerodactylia with calcinosis, there was no recognizable scleroderma.

3. The deposits usually appear subsequent to the changes in the skin, though they are sometimes seen unaccompanied by the trophic disorders of the skin.

4. The calcinosis was not limited to any one type of scleroderma.

5. The pathologic deposits of calcium vary from minute dots ("bony sand") to large fused areas, usually in the connective tissues but sometimes in the cutaneous tissues or extruding through the skin.

6. Frequent anatomic sites of deposit were the soft tissues of the phalanges and the areas around the olecranon and elbow joints.

7. Local inflammatory changes usually are not a causative factor.

8. The usual composition of the deposits was calcium phosphate and carbonate. Uric acid was never found.

9. Chemical studies do not indicate any constant variation in either the whole blood or the serum calcium values. There is no oversaturation of the calcium salts as is thought to occur in metastatic calcification.

10. The calcinosis is unlike gout, true bone formations or calcium metastases.

11. In one case with extensive generalized deposits of calcium, histologic evidence of a pathologic parathyroid process was not found at autopsy.

12. That the combination of scleroderma and calcinosis constitutes a distinct pathologic entity, despite the infrequent occurrence, is suggested by the usual location of the calcinosis, by the fairly characteristic type of deposit and by the close local relationship of the two conditions (deposits usually in areas of scleroderma).

13. It is nowise clear whether calcinosis with scleroderma results from local metabolic alterations or deranged inorganic metabolism. As in other types of pathologic calcification, the colloidal proteins are thought to play a prominent rôle.

THE BEHAVIOR OF THE PLASMA CHLORIDES IN OBSTRUCTIVE JAUNDICE*

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During the course of some observations on dogs after experimental obstructive jaundice had been produced, we were surprised at the frequency with which a reduction of the plasma chlorides occurred after complete obstruction of the duct and cholecystectomy in the same animal. The degree of reduction in the sodium chloride varied somewhat in different animals, but in all animals in which the obstruction was complete and in which the gallbladder had been removed, some depression in the amount of chlorides resulted. This behavior of the plasma chlorides may be, and probably is, only one part of an alteration in the entire physicochemical system of the animal, but it is most striking. The results here published are merely part of a more extensive study now being carried out.

In 1923, in a paper on "Observations on the Regulation of Osmotic Pressure," Gram [1] published some results of estimations on the plasma chlorides in human beings. In this work, he had further pursued the observation of himself and Norgaard [2] that a remarkable constancy of the ratio existed between the sodium chloride of the serum and the conductivity. In this further study, Gram included patients suffering from a number of diseases, among whom were several with jaundice. In his summary, he stated that:

> (*a*) Decreases of conductivity are due to changes in the salt content of the serum. . . . This decrease occurs under two circumstances: (1) A primary decrease of salts with consequent low osmotic pressure in cases with simultaneous low salt intake and the formation of exudates and transudates; (2) a secondary decrease of salts tending to keep down the high osmotic pressure caused by an increase of non-electrolytes (sugar, urea, and gall constituents). . . .

He presumed that jaundice belonged to the latter group.

In the animals used in our experiments, the degree of hyperbilirubinemia was estimated by the van den Bergh reaction. The stools were repeatedly examined for bile. At first, we had some trouble because of

* From the Laboratory of Research Surgery of the University of Pennsylvania.

1. Gram, H. C.: J. Biol. Chem. **56**:593, 1923.
2. Gram, H. C., and Norgaard, A.: J. Biol. Chem. **56**:429, 1923.

reformation of the duct continuity. This was thereafter prevented by oversewing the distal end of the duct with the omentum. The reestablishment of the bile flow to the intestine resulted in a rapid decrease in the bilirubinemia and a rise in the plasma chlorides. It will be seen

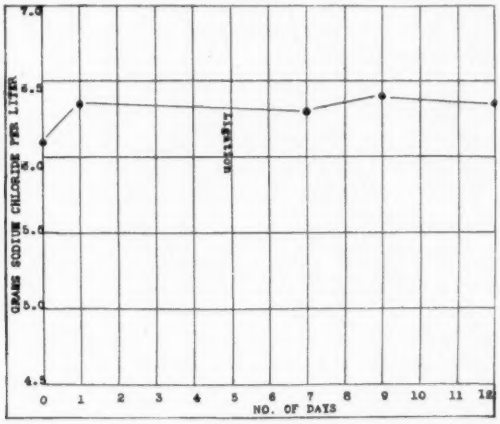

Chart 1 (dog 1).—Chloride values after simple ligation of the common duct.

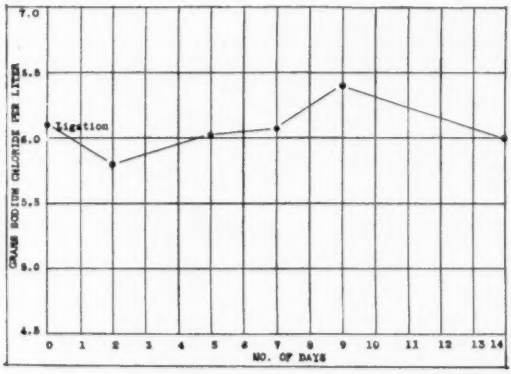

Chart 2 (dog 2).—Chloride values after simple ligation of the common duct.

from the charts that an increase in the chlorides occurred at times even before a decrease in the blood bilirubin was ascertained.

One of the most interesting features in this work was the behavior of the plasma chlorides in those cases in which the gallbladder was not removed at the time of ligation of the common bile duct. In these cases, the only decrease in the plasma chlorides was that which might occur

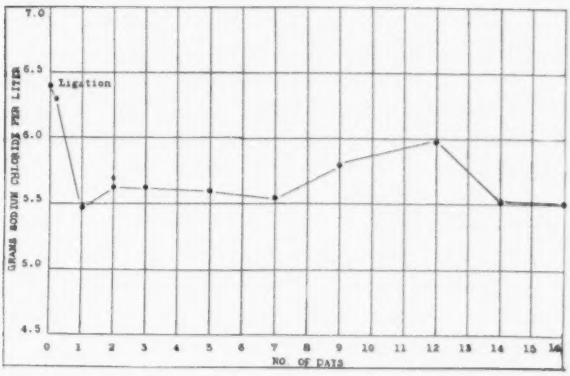

Chart 3 (dog 4).—Changes in the chloride plasma after ligation of both the cystic and the common ducts.

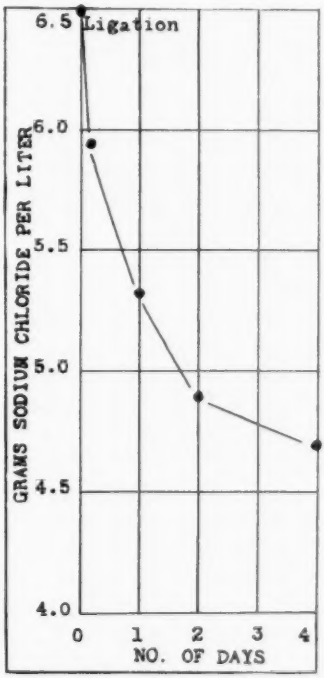

Chart 4 (dog 5).—Changes in the chloride plasma after ligation of both the cystic and the common ducts.

immediately after operation. That a decrease might be noted at a later stage of obstruction when jaundice had resulted is possible, but the behavior of the chlorides a few days after operation is entirely different from that after cholecystectomy and ligation of the common duct. In another group of dogs, the gallbladder was removed, and the flow of bile to the duodenum was not disturbed. Here, too, depression of the chlorides was not manifest. In fact, although it may occur in the normal variation of plasma chlorides, in these cases the chlorides showed a tendency to increase.

The accompanying charts illustrate the concentration of the plasma chlorides in grams of sodium chloride per liter, after three types of operations on the biliary tract of the dog. The first group (charts 1 and 2) show the chloride values after simple ligation of the common

TABLE 1.—*Concentration of Plasma Chlorides After Ligation of the Common Duct in Dogs in Group 1*

	Date	Sodium Chloride, Gm. per 1,000 Cc.	Van den Bergh	
			Direct	Indirect
Dog 1	10/ 6/26	6.11		
	10/ 7/26	6.35		
	10/11/26	Ligation of common duct		
	10/13/26	6.29		
	10/15/26	6.41		
	10/18/26	6.35		
	10/20/26	Reopened dog and explored region of common duct; found the common duct dilated and no other branch		
Dog 2	10/20/26	6.11		
	10/21/26	Ligation of common duct		
	10/22/26	5.78	Negative	Negative
	10/25/26	6.03	Negative	Negative
	10/27/26	6.07	Negative	Negative
	10/29/26	6.40	Negative	Negative
	11/ 3/26	6.00	Negative	Negative

duct. They do not show any appreciable change. Group 2 (charts 3, 4, 5, 6 and 7) give the changes in the chloride plasma after ligation of both the cystic and the common ducts. In these, it will be seen that the amount of plasma chloride decreases, usually within twenty-four hours after operation, and continues to drop, remaining low as long as a hyperbilirubinemia exists. The chlorides show a tendency to increase to within normal values even before a decrease in the bilirubinemia is manifest. Group 3 illustrates the concentrations of the plasma chloride after cholecystectomy. It will be seen that in these animals a depression of chlorides does not occur.

The plasma chlorides were determined by the method of van Slyke,[3] except in dog 15; in that case, the method of van Slyke and Donleavy[4] was used.

3. Van Slyke, Donald D.: J. Biol. Chem. **58**:523, 1923-1924.

4. Van Slyke, Donald D., and Donleavy, John J.: J. Biol. Chem. **37**:551, 1919.

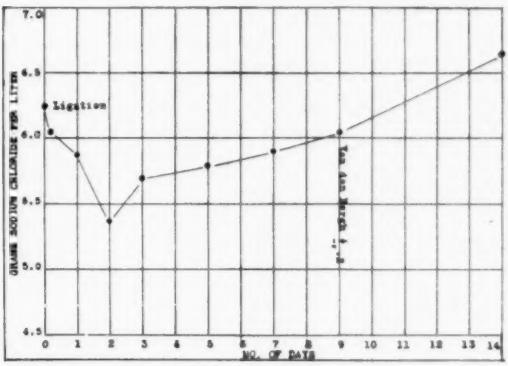

Chart 5 (dog 10).—Changes in the chloride plasma after ligation of both the cystic and the common ducts.

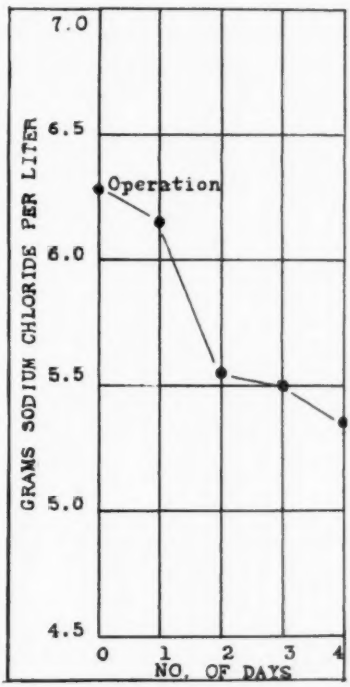

Chart 6 (dog 12).—Changes in the chloride plasma after ligation of both the cystic and the common ducts.

TABLE 2.—*Concentration of Plasma Chlorides After Ligation of Both the Cystic and Common Ducts in Dogs in Group 2*

	Date	Sodium Chloride, Gm. per 1,000 Cc.	Van den Bergh	
			Direct	Indirect
Dog 4	10/27/26, a.m.	6.41	Negative	Negative
	10/27/26, a.m.	Ligation of cystic and common ducts		
	10/27/26, p.m.	6.25	Negative	Negative
	10/28/26	5.49	Immediate	1.75 units
	10/29/26	5.63	Immediate	4.2 units
	10/30/26	5.63	Immediate	4.2 units
	11/ 1/26	5.59	Immediate	5.0 units
	11/ 3/26	5.56	Immediate	5.2 units
	11/ 5/26	5.84	Immediate	5.2 units
	11/ 8/26	5.97	Immediate	
	11/10/26	5.52	Immediate	5.0 units
	11/12/26	5.50	Immediate	
Dog 5	11/ 1/26, a.m.	6.50	Negative	Negative
	11/ 1/26, a.m.	Ligation of cystic and common ducts		
	11/ 1/26, p.m.	5.94	Immediate	1.15 units
	11/ 2/26	5.33	Immediate	1.75 units
	11/ 3/26	4.90	Immediate	2.25 units
	11/ 5/26	4.61	Immediate	4.50 units
Dog 10	12/ 1/26, a.m.	6.24	Negative	Negative
	12/ 1/26, a.m.	Ligation of cystic and common ducts		
	12/ 1/26, p.m.	6.09	Immediate	1.9 units
	12/ 2/26	5.88	Immediate	5.6 units
	12/ 3/26	5.36	Immediate	4.0 units
	12/ 4/26	5.72	Immediate	3.3 units
	12/ 6/26	5.81	Immediate	5.4 units
	12/ 8/26	5.90(stools	Immediate	4.6 units
	12/10/26	6.05 black)		
	12/15/26	6.64	Immediate	0.8 units
	At autopsy, a small duct was found which allowed fluid to pass into the lower end of the divided duct; it was rather small			
Dog 12	12/19/26, a.m.	6.28		
	12/19/26	Ligation of cystic and common ducts		
	12/20/26	6.15		
	12/21/26	5.55		
	12/22/26	5.50		
	12/23/26	5.35		
Dog 15	6/29/27	6.56	Negative	Negative
	7/ 4/27	6.54	Negative	Negative
	7/ 5/27	Ligation of common duct and cholecystectomy		
	7/ 6/27	5.68		
	7/ 7/27	5.72	Immediate	3.4 units
	7/ 8/27	5.36	Immediate	3.5 units
	7/ 9/27	4.72	Immediate	3.5 units
	7/11/27	4.86	Immediate	

TABLE 3.—*Concentration of Plasma Chloride Cholecystectomy in Dogs in Group 3*

	Date	Sodium Chloride, Gm. per 1,000 Cc.	Van den Bergh	
			Direct	Indirect
Dog 7	11/17/26	5.61	Negative	Negative
	11/17/26	Cholecystectomy		
	11/19/26	6.24	Negative	Negative
	11/22/26	6.29	Negative	Negative
	11/24/26	6.00	Negative	Negative
	11/26/26	5.74	Negative	Negative
	11/29/26	5.88	Negative	Negative
	12/ 8/26	5.99	Negative	Negative
	12/13/26	6.28	Negative	Negative
Dog 13	1/ 5/ 7, a.m.	6.19	Negative	Negative
	1/ 5/27	Cholecystectomy		
	1/ 5/27, p.m.	5.93		
	1/ 7/27	6.13	Negative	Negative
	1/ 8/27	6.08	Negative	Negative
	1/10/27	6.21	Negative	Negative
	1/12/27	6.11	Negative	Negative
	1/14/26	6.52	Negative	Negative
	1/19/27	6.46	Negative	Negative
	1/24/27	6.33	Negative	Negative
Dog 14	1/ 7/27	6.00	Negative	Negative
	1/ 7/27	Cholecystectomy		
	1/ 8/27	5.87	Negative	Negative
	1/10/27	6.28	Negative	Negative
	1/12/27	6.28	Negative	Negative
	1/14/27	6.39	Negative	Negative
	1/19/27	6.24	Negative	Negative

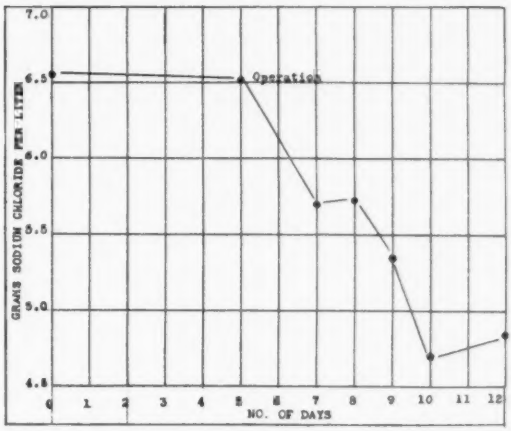

Chart 7 (dog 15).—Changes in the chloride plasma following cholecystectomy and ligation of the common duct.

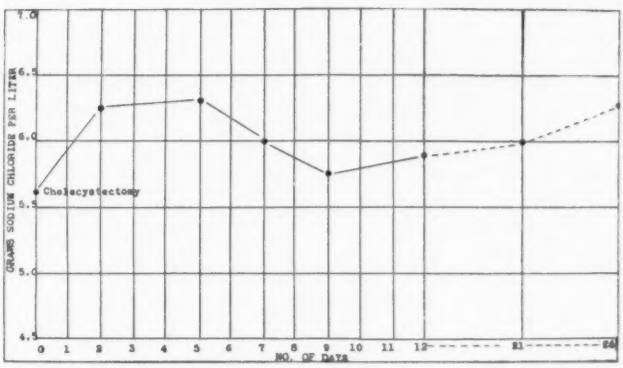

Chart 8 (dog 7).—Chloride values after cholecystectomy without ligation of the common duct.

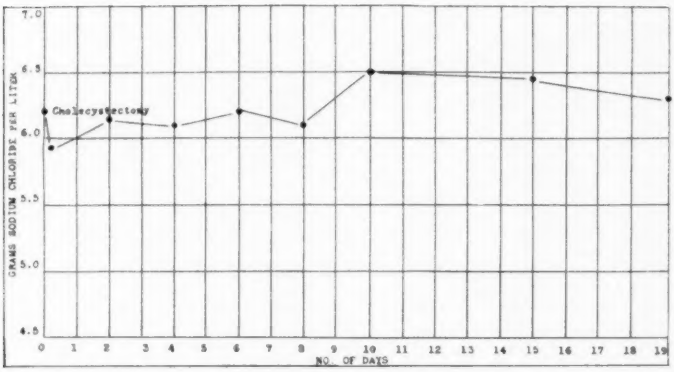

Chart 9 (dog 13).—Chloride values after cholecystectomy without ligation of the common duct.

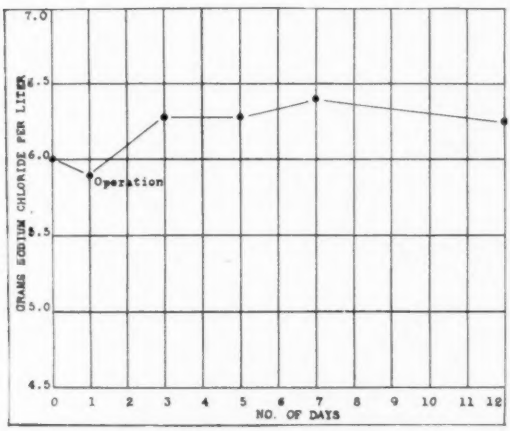

Chart 10 (dog 14).—Chloride values after cholecystectomy without ligation of the common duct.

The importance of recognizing a depression of chlorides in patients suffering from obstructive jaundice is not definitely known. It may be that in the patient who is extremely ill, the restoration of the chloride which has been depleted would be attended by less operative risk. Recently, considerable emphasis has been placed on the administration of large amounts of fluid to patients before and after operation. In many of the patients so benefited, the improvement may be the result of restoration of the sodium chloride lost during depletion.

Whether the depression of plasma chlorides which we have observed is the result of an attempt at osmotic compensation or still other factors, remains in doubt. Ni [5] recently reported an increase in the blood sugar which accompanied a primary depression of the chlorides. In obstructive jaundice, a rise in the blood sugar values has not been found in our animals, even though the chloride depression has been marked, so that the inverse ratio, as Ni calls it, between dextrose and chloride does not exist in these cases. We believe that, besides an attempted osmotic compensation, the gallbladder itself may play some part in the chloride metabolism after obstructive jaundice.

SUMMARY

Data are presented concerning the chloride metabolism after ligation of the common duct (group 1), cholecystectomy and ligation of the common duct (group 2), and cholecystectomy alone (group 3). In groups 1 and 3, depression of plasma chlorides was not found. In group 2, a reduction in the plasma chlorides occurred, varying in degree but consistently present whenever ligation was complete and the gallbladder out of the circuit.

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5. Ni, T. G.: Am. J. Physiol. **78**:158, 1926.

BRONCHOMONILIASIS

REPORT OF A CASE FROM PORTO RICO *

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AND
CHARLES WEISS, M.D.
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Bronchomoniliasis was first described as a disease entity by Castellani [1] in 1905, while he was working in Ceylon. The disease has since then been observed in various tropical, subtropical and temperate regions. Cases have been reported from India, South Africa, West Africa, Soudan, Egypt, the Belgian Congo, South America, France, southern Italy and England. Boggs and Pincoffs [2] also published records of a case from Baltimore.

ETIOLOGY

Castellani and Chalmers stated that bronchomoniliasis is generally due to *Monilia tropicalis* in Ceylon, South India and the Malay States. They expressed the opinion that the fungus is the real cause of the disease, since no other etiologic agent, such as the tubercle bacillus, is found. Moreover, when the condition improves, the fungus becomes scanty or disappears completely. Castellani [3] also described other nonpathogenic species of *Monilia* in chronic bronchitis. These species are *M. paratropicalis, M. pinoy, M. krusei* and others. We have found *Monilia psilosis (ashfordi)* in a case originating in Porto Rico.

Under the term *Monilia* is included a genus of microscopic plants belonging to the class of *Hyphomycetes* or "fungi imperfecti," the vegetative body or thallus of which appears in the lesions in the tissues (i.e., in its parasitic life), as a mass of mycelial threads or free-budding forms; some of the mycelial filaments are long and branched and often present arthrospores. An investigation of the biochemical characteristics of *Monilia* shows that it often ferments dextrose and other carbo-

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* From the Presbyterian Hospital, San Juan, Porto Rico, and the School of Tropical Medicine of the University of Porto Rico, under the auspices of Columbia University.

1. Castellani, A.: Hemorrhagic Bronchitis of Non-Tubercular Origin, Proc. Internat. Conference on Health Problem in Tropical America, Boston, United Fruit Company, 1924, p. 857.

2. Boggs, T. R., and Pincoffs, M. C.: A Case of Pulmonary Moniliasis in the United States, Tr. A. Am. Phys. **30**:474, 1915.

3. Castellani, A.; Douglas, M., and Thompson, E.: Notes on Mixed Mycotic Infection of the Bronchi, Mixed Monilia and Anaeromyces Infection, J. Trop. Med. **28**:257 (July) 1925.

hydrates with the production of acid and gas, and on the basis of these characteristics *Moniliae* have been classified by Castellani into several groups. It may be pointed out that *Moniliae* which present the same biochemical properties may differ enormously as regards pathogenicity; some produce a severe infection when inoculated into the rabbit or guinea-pig, while others appear to be harmless.

In recent years, there has been a widespread interest in the study of *Monilia* in relation to chronic diseases of the respiratory tract. Many types of yeastlike organisms have been isolated from the sputum of patients with chronic bronchitis and asthma by various investigators, particularly Kotkis, Wachowiak and Fleisher [4] of St. Louis and Steinfield [5] of Philadelphia. Relief from symptoms was obtained in many of these patients by treatment with autogenous monilia vaccines. The investigators from St. Louis assumed that "the monilia are secondary or concomitant factors, although possibly they may be the chief ones in maintaining the chronicity of the symptoms. It is possible that some irritant agent, bacterial, toxic or mechanical, may initiate in the mucosa of the bronchus certain changes as a result of which the monilia are now able to grow and maintain their existence here." At present, however, there is no agreement among writers as to what constitutes the genus *Monilia* and as to whether it has a primary or merely secondary rôle in the etiology of nontuberculous chronic bronchitis.

SYMPTOMATOLOGY

Mild, intermediary and severe types of the disease are described by Castellani. The symptoms in general are: dyspnea, cough, expectoration, with or without blood, and fever. The disease is characterized by frequent remissions and exacerbations. During the periods of remission, the fungus grows less or may entirely disappear from the sputum.

In the mild type, the patient looks well and complains of a slight cough. The expectoration is mucopurulent, yellowish, greenish or whitish and often scanty, without blood. The disease may end spontaneously within a short period or last longer, remaining stationary or passing into the severer types.

In the intermediary type, the patient complains of more or less severe cough and dyspnea, and not infrequently of subcontinuous fever. The cough comes in paroxysms and is worse in the morning and at night than in the daytime. Crises of severe hemoptysis rarely occur. Fever is

4. Kotkis, A. J.; Wachowiak, M., and Fleisher, M. S.: Relation of Monilia to Upper Air Passages, Arch. Int. Med. **38**:217 (Aug.) 1926.

5. Steinfield, E.: Bronchomycosis Associated with Certain Types of Bronchial Asthma, J. A. M. A. **82**:83 (Jan. 12) 1924; A Study of the Yeast Found in the Sputum of Patients with Asthma and Chronic Bronchitis, J. Lab. & Clin. Med. **8**:744 (Aug.) 1923.

usually absent although at times there is a subcontinuous or continuous fever. Bodily nutrition may be well maintained. The physical signs of the chest are the same as in chronic bronchitis.

The severe type of the disease runs a chronic course and almost invariably ends fatally. One or both lungs may be affected, and the pleura is frequently involved. There is cough, expectoration of blood and hectic fever. The appetite is bad and the patient looks emaciated. The course of the disease closely resembles that of tuberculosis. The physical examination of the chest reveals patches of dulness due to consolidation and pleural thickening, bronchial breathing, diminished or entirely absent vesical murmurs, crepitations, pleuritic friction sounds, and later, signs of cirrhosis of the lungs with its sequelae.

DIAGNOSIS

The diagnosis of bronchomoniliasis is based on the constant finding of a pathogenic species of *Monilia* in the expectoration of the patient. It is difficult to rule out the significance of various bacteria such as the pneumococcus, streptococcus and staphylococcus which are commonly present in the sputum. By the method of Bull and Tao,[6] it may be shown that *Monilia* will grow better in the blood of the patient than in normal controls (Weiss and Landrón[7]).

The sputum, collected after thorough rinsing of the mouth with an alkaline antiseptic solution, should be placed in a sterile Petri dish. Occasionally, *Monilia* may be seen by direct microscopic examination; usually it is best to streak the sputum (after washing it with sterile saline) over the surface of a Sabouraud dextrose agar plate, p_H 6.5, and to incubate at 35 C. for from one to four days. One should look for rather large, creamy white opaque colonies. By means of the low power objective (1/6), the colonies of *Monilia psilosis* may be seen as coarsely granular, resembling a mosaic of tiny glass marbles.

A pure colony should be transplanted to various carbohydrate mediums in fermentation tubes and into gelatin and litmus milk. Most *Moniliae* do not ferment lactose, mannite, dulcite, dextrin, the various vegetable starches or glycerin. The characteristics of *Monilia psilosis* (*ashfordi*) are given under the heading "Cultural Studies."

Intravenous injections should be made into the lung of rabbits to see if the strain of *Monilia* is pathogenic and capable of producing pulmonary lesions. Many saprophytic *Moniliae* may be encountered; these

6. Bull, C. G., and Tao, S. M.: A Method for Determining the Anti-Pneumococcal Properties of Whole Blood and the Protective Power of Immune Serum, Am. J. Hyg. **7**:648 (Sept.) 1927.

7. Weiss, C., and Landrón, F.: Immunological Studies of Tropical Sprue in Porto Rico, Am. J. Trop. Med., to be published.

do not have any etiologic relationship to bronchomoniliasis. Intravenous injections of other species of *Monilia* may kill rabbits, but fail to produce pulmonary lesions; hence, these are considered to be merely secondary invaders. The species of *Monilia* is considered by Castellani to be the real caustive agent when it produces in rabbits (on injection into the lung) a number of small pulmonary nodules showing endothelial proliferation, giant cells and *Moniliae*.

Primary bronchomoniliasis should be differentiated from the secondary type not infrequently met with in cachetic disease such as cancer, tuberculosis and diabetes. In these cases the mucous membranes of the mouth, pharynx, larynx and bronchi are covered with the fungus, whereas in genuine bronchomoniliasis the mouth and pharynx are not affected. It should be differentiated from tuberculosis by the absence of the tubercle bacillus in the expectoration, and by the negative results from inoculations into animals; from bronchospirochetosis and endemic hemoptysis by the absence of spirochetes and ova of *Paragonium westermanni*.

Prognosis is favorable in the mild cases; the intermediary types are chronic and difficult to cure, and the severe types, as a rule, end fatally.

TREATMENT

Potassium iodide is considered to be the specific in this disease, and patients with mild cases often recover with its use. Doses of from 0.5 to 1.5 Gm., well diluted in water or milk, are given three times daily. In severe cases, the drug is useless.

In connection with the use of potassium iodide, creosote and tonics, especially phosphoric and arsenical compounds, the question of nourishing food and residence in suitable climate should never be neglected. Vaccine therapy may be tried. Farah[8] obtained excellent results from the use of intramuscular injections of 2 cc. of a solution of iodized oil 40 per cent—into the gluteal region of his patients on alternate days; as many as forty injections were given without any signs of iodism. Patients with the mild and intermediary types of the condition were greatly benefited. This treatment appears to be useful in early cases before any serious damage has occurred to the lungs.

REPORT OF A CASE

History.—G. A. S., an American man, white, aged 34, married, a clerk in a stationery store, had lived in Porto Rico twelve years. He was admitted to the Presbyterian Hospital on April 23, 1926, complaining of pain in the chest, night sweats, persistent cough in the mornings with occasional expectoration of blood-

8. Farah, N.: Observations on Castellani's Bronchomoniliasis, J. Trop. Med. **26**:1 (Jan.) 1923.

tinged sputum, frequent headaches, occasional attacks of diarrhea alternating with constipation, and daily fever. During the war, he had been in the military service in Porto Rico and had suffered from a severe attack of influenza. In 1918, when discharged, he was in a poor physical condition and complained of cough, pain in the chest, shortness of breath, fever in the afternoon and night sweats. His condition was diagnosed as tuberculosis, and he went to a local sanatorium where he spent six months, most of the time in a recumbent position. He made little improvement in his general condition during this treatment and showed a daily rise in temperature. During the interval between 1918 and 1926, numerous examinations of the sputum were made for tubercle bacilli, but evidence of the bacillus was never found. The diagnosis of tuberculosis was made in this sanatorium on the basis of physical observations and roentgen-ray examinations.

The patient had had measles, whooping cough, chickenpox and diphtheria during childhood; typhoid fever had occurred at the age of 12 and malaria some time later. He had had influenza in 1917. He said that he had not had any venereal infections.

Physical Examination.—The patient was in a good state of nutrition. Examination of the chest revealed rough breathing below the angle of the right scapula and some roughness of the breath sounds at the end of inspiration in the left infraclavicular area close to the sternum. The percussion note was impaired over the upper and middle lobes of the right lung and slightly impaired over the apex of the left lung. Just below the right clavicle moist bubbling râles were heard which disappeared after coughing, but returned promptly. Bronchovesicular breathing was heard below this area. The heart was somewhat enlarged, the apex being at the sixth interspace in the anterior axillary line. Rhythm and tone were regular; murmurs were not noted.

During the two weeks of observation in the hospital, the patient's temperature was usually about 99 F., but on a few occasions it rose as high as 100.4 F. The pulse rate fluctuated from 60 to 90, and the respirations were usually about 20 per minute. The patient's weight on admission was 141.5 pounds (64.0 Kg.) and was the same when he left the hospital.

Since his discharge from the Presbyterian Hospital in 1926, the patient has been under observation in the clinic. He has continued his work and has refused to take any medical treatment. About two months prior to presentation (Jan. 27, 1928), he had had an attack of hemoptysis. Laboratory and roentgen-ray examination still failed to reveal any evidence of tuberculosis. *Moniliae* were present in abundance in the sputum.

Laboratory Examination.—Urinalysis revealed an acid reaction; specific gravity, 1.027, and an absence of albumin, sugar and casts, and abnormal constituents in the sediment.

Examination of the feces on April 23, 1926, showed *Trichuris trichiura* eggs to be present; an examination on June 7, 1927, revealed *Monilia psilosis* isolated on Sabouraud dextrose agar plate.

Examination of the blood on April 23, 1926, showed: red blood cells, 4,400,000; white blood cells, 8,100; hemoglobin, 80 per cent; polymorphonuclears, 70 per cent; mononuclears, 30 per cent.

An examination on April 29 showed: white blood cells, 9,700; polymorphonuclears, 64 per cent; eosinophils, 9 per cent; mononuclears, 24 per cent; transitionals, 2 per cent.

Examination on Jan. 26, 1928, showed: red blood cells, 3,300,000; white blood cells, 7,800; hemoglobin, 70 per cent (Dare); polymorphonuclears, 66 per

cent; small lymphocytes, 30 per cent; large lymphocytes, 2 per cent, and transitionals, 2 per cent (100 white blood cells counted).

A chemical examination of the blood on May 27, 1927, revealed: sugar, 125 mg. per hundred cubic centimeters; urea nitrogen, 7 mg. per hundred cubic centimeters; uric acid, 4.2 mg. per hundred cubic centimeters; creatinine, 1.5 mg. per hundred cubic centimeters.

Bacteriologic examination of specimens of sputum taken at daily intervals for one month (from May 7, 1926, to June 5, 1926) were negative for tubercle bacilli. On June 10, 1927, several specimens were again examined by the direct and antiformin methods and found negative for tubercle bacilli. Cultures of the sputum on Lubenau's medium were also negative. Pneumococci, streptococci and staphylococci were isolated. Dark-field examination did not reveal any spirochetes.

Cytologic examination of the sputum revealed large round cells and also much mucous and bronchial epithelium; a few red blood cells and white blood cells were seen.

Mycologic examination of the sputum using Sabouraud agar gave several colonies of *Monilia psilosis* on numerous occasions. On June 20, 1927, specimens of the patient's sputum, treated with antiformin, were inoculated into two guinea-pigs. They did not show any signs of tuberculosis for four months. On June 24, 1927, 2 cc. of a saline emulsion made from a three day old culture of *Monilia psilosis* isolated from the patient's sputum was injected intravenously into a rabbit. The animal died on the sixth day.

Postmortem examination revealed congestion of the lungs and large white kidneys. *Moniliae* were isolated from these organs.

Microscopic examinations of the tissues of the animal were made by Dr. R. A. Lambert, Professor of Pathology, and Director of the School of Tropical Medicine of the University of Porto Rico. He reported as follows:

"Acute destructive inflammatory foci are found in the lung, kidneys and tongue. The lung shows a widespread oedema, small poorly defined foci, with necrosis and polynuclear infiltrations in the center surrounded by a zone in which there is mononuclear infiltration and epithelial and connective tissue proliferation. The kidney shows more marked inflammatory changes, though quantitatively like those in the lung. In some of the suppurative foci clumps of yeast-like structures are easily recognized by their pale basic stain, well defined cell membrane and double contour. Many of the tubules are filled with pus. Proliferative changes are marked. The liver presents fatty changes of moderate degree, but no focal inflammatory lesions. The spleen and heart are negative. The section of tongue includes a small area of ulceration covered by a membranous exudate.

Diagnosis: Acute focal inflammatory lesions of tongue, lung and kidney. (Experimental Moniliasis.)

On Jan. 20, 1928, the patient coughed into a Petri dish containing Sabouraud medium. A few colonies of *Monilia* were found. On Jan. 26, 1928, the patient expectorated a thick viscid sputum with much visible blood. Microscopically, a mass of leukocytes and red blood cells were seen embedded in mucus. Tubercle bacilli could not be demonstrated by either direct smear or the antiformin methods. The results of inoculation into guinea-pigs for tubercle bacilli were negative. (The animals were observed for three months.)

Cultural Studies.—Moniliae which we isolated conformed in every way to the description given by Ashford. The latter corroborated our mycologic observations in this case. The colonies on Sabouraud dextrose agar were thick cream-colored.

If cultivated for several weeks on the surface of a Sabouraud slant, the culture assumed the appearance of a cameole with delicate arborizations extending into the substance of the medium.

Yeastlike oval forms were readily found in young as well as in old cultures. These had a definite capsule containing hyaline plasma with a vacuole containing one or more actively motile bodies. Mycelial threads were obtained by digging into the agar with the platinum loop; these presented subdivisions by means of septums and often motile bodies. Budding cells were also seen.

The following is a summary of the behavior on various mediums: In Sabouraud dextrose agar (p_H 6.5), there were typical, creamy elevated colonies. In gelatin there was no liquefaction; an inverted pine tree was present. In litmus milk, there was no coagulation and the medium became progressively more alkaline. In dextrose, maltose, d-mannose or raffinose broth, acid and gas were produced. Acid production was delayed in saccharose and galactose and acid in xylose broth. There was no liquefaction in Loeffler's coagulated beef serum. In Russel's double sugar: the butt was slightly acid, the slant, alkaline. In lead acetate agar, the butt was negative; the slant showed brown discoloration. The organism grew well in a J. Howard Brown anerobic jar, and produced active fermentation of maltose under a petrolatum seal.

Roentgen-Ray Examination.—A roentgen-ray examination on Nov. 27, 1922, by Dr. Roses Artau, showed the right pulmonary shadow excessively accentuated. The glands were enlarged; there was nuclear condensation. There was possible apical pleurisy on the right side.

On March 31, 1923, both apexes were slightly less transparent. There were increased hilum shadows with diffuse infiltration of both lungs.

On Sept. 19, 1923, there was slight infiltration of both apexes and increased hilum shadows. The peribronchial nodes were calcified.

On June 23, 1925, the bases and apexes were normal. The hilum shadows had increased, and there was slight fibrosis with discrete mottling.

On Dec. 28, 1925, there was slight mottling of the median lobe of the right lung.

The last examination on Jan. 27, 1928, was taken during a period of exacerbation of the patient's symptoms, while he was in poor general health and suffering with daily afternoon rise in temperature and expectorating a thick viscid sputum containing much free blood and many cells and *Monilia*. There was extensive peribronchial infiltration with apparent calcification of glands near the hilum. The parenchyma was mottled throughout both bases with several small abscesses in the middle lobe of the right lung. There was a marked thickening of the pleura on the left side. The apex of the left lung was clear; the right was slightly cloudy. The heart shadow was slightly increased.

SUMMARY

A case of pulmonary moniliasis is reported occurring in a white American man, who has been living in Porto Rico for twelve years. The symptoms simulate chronic pulmonary tuberculosis, but repeated examinations of the sputum over a period of ten years by direct microscopic and antiformin methods as well as by animal inoculation have failed to show the presence of tubercle bacilli. On the other hand, there is always present in the sputum a yeastlike organism of the genus

Monilia psilosis (*ashfordi*), which is pathogenic for guinea-pigs and rabbits, and produces necrosis of the lung with mononuclear infiltration and connective tissue proliferation on intrapulmonary injection into rabbits. These animals usually die within six days and show a general moniliasis with inflammatory lesions of the tongue, lungs and kidneys.

These laboratory observations together with the results of the roentgen-ray examinations and the clinical history of the case lead us to regard this as a case of bronchomoniliasis. That *Moniliae* are the primary cause of the disease and not secondary invading organisms which contribute to the chronicity of the disease and its toxic symptoms has not been absolutely proved.

SOME OBSERVATIONS ON THE SCAPULAE OF THE CHINESE*

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In 1906, Graves began his observations on scapular types and their relation to morbidity in the individual subject. Since then, in numerous papers he [1] has presented the results of his studies, which include a classification of scapulae according to their vertebral borders, as convex, straight and concave. The last two types he grouped together and called scaphoid. In them, he found that the bone is longer, the inferior angle more acute and the spine more horizontal. The classification of scapulae according to age periods showed a striking decrease in the incidence of the scaphoid type as old age was approached. This he explained as due either to a change from the scaphoid to the convex type, as the individual grew older, or to a greater mortality among those with the scaphoid type of scapula. Examination of the scapulae of the fetuses showed definite types as early as the tenth week, and repeated observations on persons over periods of years did not disclose any change in the individual scapular form. This convinced Graves that the scapular characteristics for persons do not vary with age, and that the scaphoid type of bone is an indication of increased susceptibility to disease and occurs among those he calls the "potentially sick" of the race. According to Graves, scapular forms are hereditary, and are an indication of longevity and of morbidity in general. At one time, he thought that the scaphoid scapula might be an indication of syphilis in the ascendants, and a sign of general degeneration.

The investigations of Warburg,[2] Cunningham,[3] Kollert,[4] Chotzen [5] and others confirm the observations of Graves concerning the frequency of scaphoid scapulae in general and its decreasing frequency in the

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1. Graves, W. W.: J. Cutan. Dis. **31**:241, 1913. The Relations of Scapular Types to Problems of Human Heredity, Longevity, Morbidity and Adaptability in General, Arch. Int. Med. **34**:1 (July) 1924; Methods of Recognizing Scapular Types in the Living, ibid. **36**:51 (July) 1925; The Plus-Potentially Sick of the Race, Glasgow, Alexander Macdougall, 1925; The Relation of the Shoulder Blade Types to Problems of Mental and Physical Adaptability, London, Oliver & Boyd, 1925.

2. Warburg: Med. Klin. **9**:1851, 1913; Klin. Wchnschr. **2**:31, 1919.

3. Cunningham, R. L.: The Scaphoid Scapula, Arch. Int. Med. **10**:589 (Dec.) 1912.

4. Kollert: Wien. klin. Wchnschr. **24**:1299, 1911.

5. Chotzen: Klin. Wchnschr. **55**:949, 1918.

succeeding age periods. Regarding the question of interpretation, however, some writers, especially Warburg and Cunningham, do not agree. They are of the opinion that the scaphoid scapula is simply a normal variation from the usual convex type. It is interesting to note that these observers examined persons in only one age period (Warburg from 6 to 7 years; Cunningham from 16 to 25 years) and could not find any signs of degeneration, either physical or mental, in persons with scaphoid scapulae when compared with those with convex scapulae. Cunningham's observations were made on college and university students, and she feels that if there is any difference in mental capacity between those having convex and scaphoid types, the advantage is in favor of the latter.

There does not seem to be any doubt about the existence of a progressive decrease in the incidence of scaphoid scapulae in succeeding age periods and, as Graves says, there can be only two possible explanations: either the scaphoid type is converted into the convex type, or many of the scaphoid group are eliminated through death. He believes that there is evidence to show that the scapular type is determined early in fetal life and probably continues without change in type throughout the life of the person. Curtius,[6] on the other hand, states that his observations support the view of change of the scapular form, in that he found relatively few scaphoid forms at birth and a rapid increase in incidence with advancing age, followed by a falling off again as adult life is reached. He feels that rickets and muscular pull determine the type, except for the rare congenital cases. Those with scaphoid scapulae also showed other stigmas of rickets. Regarding muscular pull, he believes that if the infraspinatus—subscapularis—serratus anterior group is stronger than the rhomboid group, the concave type will result; if they are equal, the straight type will predominate, whereas, if the rhomboids are the stronger, a convex border will result. Granting that this explanation is correct, there is still the fact of the decreasing incidence of scaphoid scapulae with each decade of life to explain. Unless there is a change in the form of the scapular vertebral border after adult life, which is scarcely conceivable, there must be a higher rate of mortality among bearers of the scaphoid type.

In order to determine the occurrence of scapular types and their incidence among the Chinese, observations were made on 546 persons ranging from 15 to 78 years of age. The observations were made according to Graves' method of palpation. In a large number of cases, roentgenologic examinations were made for confirmation. These were made only on adults, however, in order to be sure that the vertebral border was ossified.

6. Curtius, F.: Deutsche Ztschr. f. Nervenh. **92**:101, 1926.

Of the 546 cases, 258 or 47.2 per cent of the subjects had convex scapulae; 194, or 35.4 per cent, had straight scapulae, and 94, or 17.4 per cent, had concave borders. Convex scapular vertebral borders were, therefore, found in 47.2 per cent of the cases compared with 52.8 per cent of the scaphoid type. Examinations were not made of persons under 15 years of age. According to age periods, there was an extremely definite drop in the incidence of the scaphoid type with each decade, as is shown by the accompanying table. There was not only a decrease in the frequency of the concave type but also a decrease definitely in the straight type.

In classifying the scapulae observed, it was found that 94, or 17.4 per cent, were of the mixed type and were practically always either convex and straight or concave and straight, only 3 being combined convex and concave. In these cases, those with one convex scapula were classified as convex, and those with one concave scapula were classified with the concave.

Age Incidence of Scaphoid Scapulae

Age	Convex, Per Cent	Scaphoid, Per Cent
15-20	17.9	82.1
21-30	41.5	58.5
31-40	47.3	52.6
41-50	63.0	37.0
51-60	72.7	27.2
60 +	84.6	15.4

One hundred and ninety-two of the 546 persons examined had Wassermann and Kahn tests of the blood, and of these the tests for only 16 were positive. Ten of the 16 positive reactions occurred in patients with convex scapulae and 6 in patients with scaphoid scapulae.

Of 305 persons whose lungs were found normal by roentgen-ray examination, 55 per cent had scaphoid scapulae. Fifty-two per cent of 109 cases diagnosed as pulmonary tuberculosis were shown by roentgenologic examination to be present in patients with convex scapulae. From these observations on the pulmonary conditions of 414 persons, it does not seem justifiable to say that, in general, persons (Chinese) with scaphoid scapulae are more susceptible to pulmonary tuberculosis than are other persons.

The etiology of scaphoid scapula was not brought out by these observations, but the progressive decline in the percentage of the scaphoid type of scapula with each succeeding decade of age seems definitely to indicate a greater mortality among persons with this type of scapula. It seems inconceivable to me that there can be a change in the shape of the bone after maturity has been reached.

There was nothing in these observations to indicate degeneracy among persons with scaphoid scapulae.

SUMMARY

Five hundred and forty-six Chinese were observed for scapular types.

A definite decrease in the incidence of scaphoid scapula with each succeeding decade of life was found, which is interpreted as indicating an increased mortality among persons with scaphoid scapulae.

No relation was found between scaphoid scapula and syphilis in the individual as revealed by the Wassermann and Kahn reactions.

The absence of pulmonary tuberculosis was just as frequent among bearers of scaphoid scapulae as among those with the convex type of scapula, and conversely; pulmonary tuberculosis was as frequent in persons with convex scapulae as in those with the scaphoid type of scapula.

THE ELECTROCARDIOGRAM IN HYPERTENSION*

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Chronic disease of the heart muscle, often called "chronic myocarditis," is the most common type of heart disease found in patients after the age of 40. Hypertension, which is present in about 75 per cent of the cases, is believed to be the most constant and the most important factor in causing this condition. The changes produced in the heart muscle as a result of hypertension are not always recognized clinically, and often it is only through electrocardiographic examination that the condition is detected.

To determine the significance, therefore, of the electrocardiographic observations in hypertensive heart disease, a study was made of 100 consecutive patients with hypertension who presented themselves for treatment at the heart clinic of the medical dispensary of the University of Minnesota. A thorough physical examination, a roentgen-ray examination and an electrocardiographic examination were made in each case.

In 37 of the cases (37 per cent), abnormal signs were not noted in the electrocardiogram. According to the roentgen-ray examination, the heart was normal in size in 21 of the 37 cases and enlarged in 16 cases. The enlargement varied from a slight degree in 12 to a marked degree in 4 cases. The blood pressure was 200 or over in 13 of the 21 pateints with normal sized hearts, and 8 had a pressure under 200; 8 of the 16 patients with enlarged hearts had a blood pressure of 200 or over.

Sixty-three of the 100 patients showed some abnormality in the electrocardiogram. Extrasystoles were noted in 12 cases. These were divided as follows: auricular, 1; nodal and auricular, 1; interpolated, 1; right ventricular, 4; left ventricular, 4; and right and left ventricular, 1. In 6 of the 12 cases with extrasystoles signs of myocardial damage were noted, such as negative T waves in leads I and II, delayed conduction, etc.

A delay in conduction was noted in 5 of the abnormal cases. In 3 cases there was a delayed intraventricular conduction, in 1 a delayed auriculoventricular conduction and in 1 a delay of both auriculoventricular and intraventricular conduction.

An inversion of the T wave in one or more leads was found in 20 cases, in 5 of which it occurred in lead I; in 9 cases in lead I and II, and in 6 cases in lead II and III.

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The average known duration of the existence of hypertension in the cases showing evidence of damage to the heart muscle was approximately five years, as compared with an average known duration of four years in the negative cases.

The range of the blood pressure in this group showed 15 patients with a systolic pressure below 200 and 10 with a systolic pressure of 200 or over.

Left ventricular preponderance was noted in 44 of the 100 patients in this series (44 per cent), while 56, or 56 per cent, did not show any preponderance. That so great a percentage of the patients should not show left ventricular preponderance was surprising. Various factors were therefore investigated as to their relationship to preponderance. The size of the heart, the ratio between the median right and median left diameters of the heart, the duration of the hypertension, the height of the blood pressure and the condition of the heart muscle, all were studied as to their relation to preponderance.

In the 56 cases which showed negative electrocardiograms, the heart was hypertrophied in 32 cases (57 per cent) and normal in 24 (43 per cent). Of the 32 hypertrophied hearts, 19 were slightly enlarged, 9 moderately enlarged and 4 greatly enlarged. In the 44 cases which showed left ventricular preponderance, the heart was hypertrophied in 32 cases (73 per cent) and normal in 12 (27 per cent). Of the 32 hypertrophied hearts, 11 were slightly enlarged, 16 moderately enlarged and 5 greatly enlarged.

Of the 36 normal sized hearts in the entire group of 100 cases, 12 (33 per cent) showed left ventricular preponderance and 24 (67 per cent) did not. Of the 64 hypertrophied hearts, 32 (50 per cent) showed left ventricular preponderance.

If these 64 cases are grouped according to the extent of the enlargement, it is found that of 30 cases in which slight enlargement occurred, 19 (63 per cent) did not show preponderance and 11 (37 per cent) did. Of the 25 cases which showed a moderate enlargement of the heart, 9 (36 per cent) did not show preponderance and 16 (64 per cent) did. Of the 9 cases with marked enlargement of the heart, left ventricular preponderance was present in 5 cases (55 per cent) and absent in 4 (45 per cent). Although left ventricular preponderance was present in only 50 per cent of the cases with enlarged hearts, these figures show that the frequency of preponderance tends to increase as the enlargement of the heart increases to a moderate degree, and then tends to decrease as the heart becomes markedly enlarged.

The ratio between the median right diameter and the median left diameter of the heart was studied as to its bearing on left ventricular preponderance. Although the ratio between these diameters does not give a true comparison between the relative size of the right and the

left side of the heart, yet the relative value of the ratio was considered to be approximately indicative of the corresponding enlargement of the right and the left side. The results are shown in tables 1 and 2.

If the M R : M. L. ratio can be taken as an index of the comparative ratio between the size of the right and the left side of the heart, these results would tend to show that there is not a definite relationship between the comparative enlargement of the right and of the left side of the heart and left ventricular preponderance, although here again the tendency to preponderance is greater in the group showing a M R : M L ratio under 50 per cent.

The duration of the existence of hypertension was noted as to its effect on preponderance. It was difficult to obtain correct estimates of the duration of the hypertension as many of the patients had not

TABLE 1.—*Group Which Showed Negative Electrocardiograms (56 Cases)*

		$\frac{M R}{M L}$ Ratio Under 50%			$\frac{M R}{M L}$ Ratio Over 50%		
	Total No.	No.	Per Cent	Average Ratio	No.	Per Cent	Average Ratio
Normal sized hearts	24	12	50	43%	12	50	61%
Enlarged hearts	32	15	47	41%	17	53	60%

TABLE 2.—*Group Which Showed Left Ventricular Preponderance (44 Cases)*

Normal sized hearts	12	7	58%	43%	5	42%	56%
Enlarged hearts	32	25	78%	38%	7	22%	57%

known of the presence of hypertension or had received no medical attention before coming to the clinic. Of those who did know of the presence of hypertension, the duration since first discovered by medical examination was taken as the known duration. It is more than likely that most of these patients had hypertension long before it was discovered by medical examination.

The average duration of the existence of hypertension in the group of patients who did not show any preponderance was 4.55 years in those with hypertrophied hearts and 5.45 years in those with normal hearts.

In the group showing left ventricular preponderance, the duration was 4.8 years in the patients with normal sized hearts and 4.5 years in the patients with enlarged hearts.

Comparatively, the two groups do not show any difference in the time element with respect to preponderance.

That a definite relationship does not exist between the height of the blood pressure, size of the heart and left ventricular preponderance

is shown in table 3. There is little difference in the range of the blood pressure in the various conditions noted. In the cases in which there was left ventricular preponderance, 11 patients (25 per cent) had a systolic blood pressure of 200 or over, and 33 (75 per cent) a systolic pressure under 200. In the group not showing a preponderance, 31 (55 per cent) had a systolic blood pressure of 200 or over and 25 (45 per cent) a systolic pressure under 200. Thus it will be seen that blood pressure alone is not a factor in the production of left ventricular preponderance; in fact, the higher the blood pressure, the less the likelihood of preponderance. A left ventricular preponderance was found in only 11 of 42 cases with a systolic pressure of 200 or over.

When one notes the combined effect of hypertension plus an enlarged heart, it is found that in the group of patients with normal sized hearts, only 1 patient with a systolic pressure over 200 showed left ventricular preponderance, while 10 with a systolic pressure below 200 (between 150 and 200) showed left ventricular preponderance. In the group with enlarged hearts, the effect of enlargement plus hypertension in the production of left ventricular preponderance is noted only when the enlargement increases to a moderate degree. Then only is preponderance present in almost an equal number of instances in patients with a systolic pressure of 200 or over as in those with a systolic pressure between 150 and 200 (9 cases below 200 and 7 cases over 200). When the enlargement becomes marked, there is again a lessened tendency to preponderance with a systolic pressure over 200.

The diastolic pressure has been considered by many observers as indicative of the condition of the myocardium, a relatively high diastolic pressure indicating a poor myocardium and vice versa.

The relationship between diastolic pressure and left ventricular preponderance was observed in this series. A diastolic pressure of 90 was taken as the dividing line. In the group of patients showing left ventricular preponderance, 28 (64 per cent) had a diastolic pressure over 90 and 16 (36 per cent) had a diastolic pressure of 90 or under. In the group which did not show preponderance, 32 patients (57 per cent) had a diastolic pressure over 90 and 24 (43 per cent) a diastolic pressure of 90 or under. It will be seen, therefore, that there is practically no difference in the diastolic pressure in the two groups.

The condition of the myocardium was again investigated with respect to preponderance by means of the other electrocardiographic changes noted. It is known that delayed conduction intervals and negative T waves indicate myocardial degeneration and coronary disease. Whether these pathologic changes in the heart muscle would affect the electrocardiogram with respect to preponderance was noted. Twenty-five cases showed electrocardiographic evidence of myocardial damage. Left

ventricular preponderance was found in 13 (52 per cent) of these cases and in 12 (48 per cent) it was absent. It can be stated, therefore, that the condition of the myocardium as shown by the electrocardiogram does not have any effect on the production of left ventricular preponderance.

COMMENT

From the observations noted, it will be seen that the electrocardiogram does not give any definite information as to the effect of hypertension on the functional efficiency of the myocardium until a true myocardial degeneration has taken place. Then, of course, the electrocardiogram will show evidence of heart muscle disease which

TABLE 3.—*Blood Pressure Range, According to Size of Heart and Presence or Absence of Left Ventricular Preponderance in the Electrocardiogram*

Systolic Blood Pressure	150	160	170	180	190	200	210	220	230	240	250	260	Total Cases
Normal sized hearts without left ventricular preponderance.	2	2	6	1	2	4	4	2	1	0	0	0	24
Normal sized hearts with left ventricular preponderance....	3	0	4	2	2	0	0	0	0	1	0	0	12
Enlarged hearts, 1st degree without left ventricular preponderance	1	1	2	4	2	3	2	1	2	0	0	1	19
Enlarged hearts, 1st degree with left ventricular preponderance	1	2	1	5	0	1	0	1	0	0	0	0	11
Enlarged hearts, 2nd degree without left ventricular preponderance	0	0	0	0	2	2	1	2	1	0	0	1	9
Enlarged hearts, 2nd degree with left ventricular preponderance	0	2	1	1	5	1	0	2	0	3	0	1	16
Enlarged hearts, 3rd degree without left ventricular preponderance	0	0	0	0	0	0	0	2	1	1	0	0	4
Enlarged hearts, 3rd degree with left ventricular preponderance	0	1	0	1	2	0	0	0	0	1	0	0	5

cannot be detected in any other way. How soon these signs will appear cannot be determined by the height of the blood pressure, the enlargement of the heart or the character of the electrocardiogram. In 37 per cent of the cases in this series, the electrocardiogram was negative; among these were cases in which the heart was normal sized and those in which it was markedly enlarged, cases with mild hypertension and with extreme hypertension. There was practically no difference in the duration of the hypertension in the electrocardiographically negative hearts and in the positive ones.

There were fewer cases in which there was a systolic blood pressure over 200 in the electrocardiographically positive hearts than in the negative ones.

The question of left ventricular preponderance brings forth some interesting deductions. When Einthoven first began to use the electrocardiogram in the study of heart disease, he noticed that hypertrophy

of one or the other ventricle produced characteristic electrocardiographic signs. Lewis,[1] however, noted that these changes were not invariably found. He sought the explanation of these difficulties in a study of the relative weight of the two ventricles under various circumstances. He devised a method of sectioning the heart by which the weight of the muscle of each ventricle could be determined separately. The ratio of the weight of the left ventricle to the weight of the right ventricle (L:R) was then determined. He found that this ratio varied greatly and the occurrence of signs of preponderance in the electrocardiogram were attributed to this variance. Hermann and Wilson,[2] following Lewis' method, except for some minor alterations in the technic, studied a series of fifty-nine cases with regard to the effect of hypertrophy on preponderance. They concluded that the relative weight of the two ventricles is only one of many factors which influence the form of the ventricular complex of the electrocardiogram and that its influence predominates only when the heart is greatly hypertrophied. Cohen[3] showed by a series of experiments that the position of the heart in the chest has a far reaching effect on the form of the electrocardiogram. He expressed the belief that the combined influence of the position of the heart and the type of hypertrophy influence the form of the electrocardiogram.

It is known that lesions in the main branches of the bundle of His produce curves similar to those of preponderance. Wilson and Hermann have also shown that lesions which delay the passage of the impulse through one of the bundle branches may produce curves which closely resemble preponderance curves. They do not believe that all preponderance curves are produced in this way. They suggested that possibly variations in the arrangement of the conducting system may have something to do with the form of the electrocardiogram. Both ventricles do not receive the impulse at the same time, and it is probable that in preponderance curves the precedence of one ventricle over the other may be unusually great.

The clinical study of these various factors in this series of cases tends to show that while hypertrophy of the left ventricle and a relative disturbance of the L:R ratio are factors in the production of left ventricular preponderance, they are not determining factors, as 38 per cent of the hearts which showed preponderance were not enlarged and 57 per cent which did not show preponderance were enlarged. That

1. Lewis, T.: Observations upon Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber, Heart **5**:367, 1913-1914.

2. Hermann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Postmortem Observations, Heart **9**:147 (April) 1922.

3. Cohen, Alfred E.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, Heart **9**:311 (Dec.) 1922.

the hypertension was not a factor is shown by the study of the blood pressure range in the various groups of this series. Only 44 per cent of the cases showed preponderance. That hypertension may have a deterrent effect in the production of preponderance is shown by the fact that, in the group with normal sized hearts, only one case with a systolic blood pressure over 200 showed left ventricular preponderance, while ten cases with a systolic pressure between 150 and 200 showed preponderance.

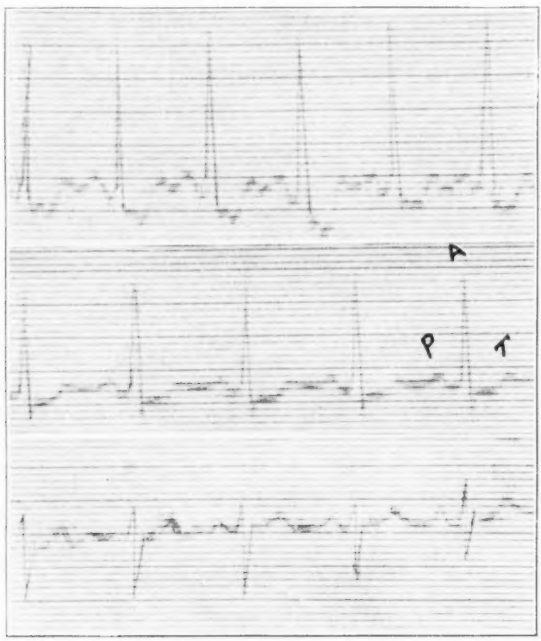

Chart 1.—Electrocardiogram of a patient taken Jan. 23, 1924, showing left ventricular preponderance.

Whether delayed conduction had any bearing on the curve of preponderance cannot be stated, although none of the cases with delayed conduction showed left ventricular preponderance. Of all the cases with evidence of myocardial damage as shown by delayed conduction and negative T waves, only 52 per cent showed preponderance.

That there are other factors involved in the production of left ventricular preponderance may be assumed from the following instances: In charts 1, 2 and 3 the tracings taken at different intervals show first left ventricular preponderance, then no preponderance and finally prepon-

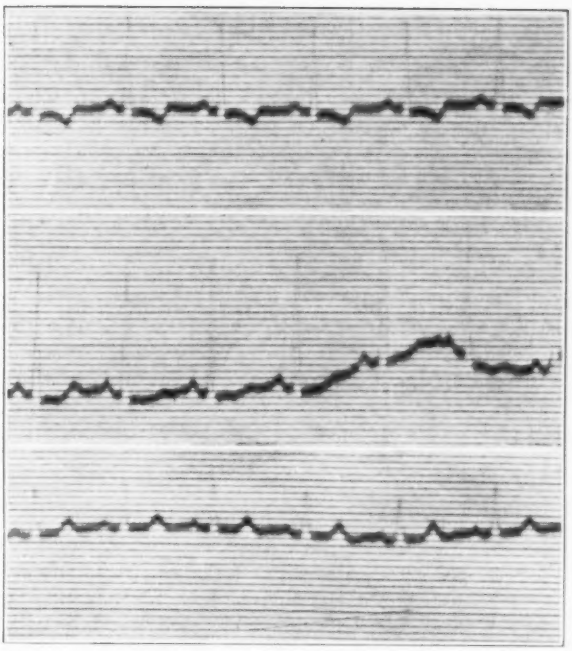

Chart 2.—Electrocardiogram of same patient taken Oct. 29, 1926, showing no left ventricular preponderance.

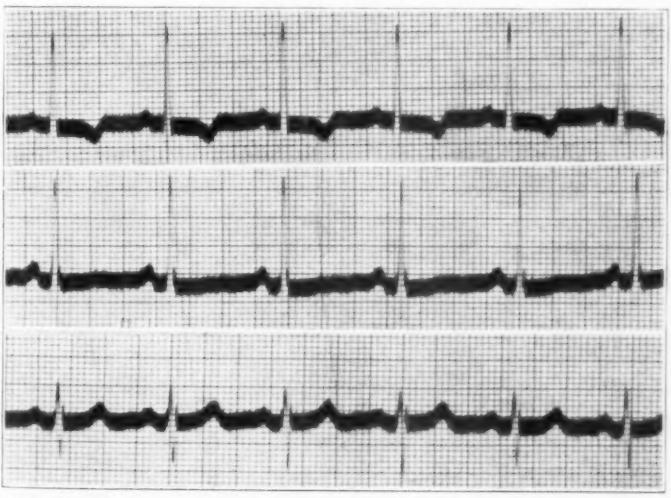

Chart 3.—Electrocardiogram of same patient taken April 6, 1927, again showing left ventricular preponderance.

derance again. During the period involved, the size of the heart has remained practically the same as shown by the roentgen-ray examinations. The blood pressure has remained constant and the clinical symptoms have not changed.

It has been shown that left ventricular preponderance of the heart in myxedema disappears after thyroid medication.

SUMMARY AND CONCLUSIONS

1. The electrocardiogram per se does not give any definite information as to the effect of hypertension on the heart until a myocardial degeneration has taken place.

2. The interval after which this occurs cannot be determined clinically.

3. Left ventricular preponderance is not always present in hypertensive heart disease. It was noted in only 44 per cent of this series.

4. Left ventricular hypertrophy, while a factor in causing left ventricular preponderance, is not a determining factor.

5. The frequency of left ventricular preponderance tends to increase as the enlargement of the heart increases to a moderate degree, and then tends to decrease when the heart becomes markedly enlarged.

6. There is no definite relationship between the comparative enlargement of the right and left side of the heart, as indicated by MR : ML ratio and left ventricular preponderance. The tendency to left ventricular preponderance is greater, however, in the group showing a MR : ML ratio under 50 per cent.

7. The duration of the existence of hypertension does not have a bearing on left ventricular preponderance.

8. Hypertension alone does not produce preponderance. In fact, the tendency is the other way; the higher the blood pressure, the less likelihood of left ventricular preponderance.

9. The condition of the myocardium as shown by other electrocardiographic changes does not influence the production of left ventricular preponderance.

10. Other factors, besides those enumerated, and at present unknown, are involved in the production of left ventricular preponderance.

ULCERATION OF THE ESOPHAGUS

EXPERIMENTAL STUDY *

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MAURICE FELDMAN, M.D.
AND
WAITMAN F. ZINN, M.D.
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In the course of our clinical study of ulceration of the esophagus, it was evident that, up to the present, insufficient attention has been directed to this disease, which according to our experience is more common than has ordinarily been reported in the literature. On this account, an attempt was made to determine experimentally certain important diagnostic problems associated with this condition.

In our experiments, nineteen dogs were utilized. The dog is a favorable subject for experimental study of this disease, as ulcerations can be produced with but slight difficulty following which x-ray and esophagoscopic examinations can be readily performed.

The following types of ulcerations were produced: (1) mucosal lesions; (2) penetrating ulcers; (3) perforating ulcers.

METHOD OF PRODUCTION OF ULCERS

As our study of ulcerations of the esophagus was undertaken primarily with the object in view to clear up certain questions in diagnosis, it made but slight difference as to the method of the formation of the ulcer. On this account, traumatic ulcers were produced by means of a biting instrument passed through the esophagoscope. At first, mucosal erosions were produced by scarification of the mucous membrane, but as these ulcers healed too rapidly, they were unsatisfactory for study. Even following a single application of phenol or lye on the small eroded area, healing occurred so rapidly that signs of the lesion did not remain after a week. It was then decided to produce deep penetrating ulcers which would probably remain unhealed for a longer period and would therefore be more adaptable for this study. These were produced by removing deep portions of tissue. These ulcerations also had a tendency to heal rapidly, though they would remain unhealed for a longer period than the superficial mucosal erosions.

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* From the Gastro-Enterological Clinic of the Department of Medicine and the Pharmacological Laboratory of the University of Maryland.

* Read at the meeting of the Association of American Physicians in Washington, May 3, 1928.

In an attempt to produce chronic ulcers simulating chronic peptic ulcerations of the esophagus, we administered large quantities of a 10 per cent solution of hydrochloric acid through a tube following the production of these lesions. Two drachms (7.5 cc.) of the acid was administered four times daily for varying periods extending over several days to several months. Interesting results were obtained in this study, as the mucosal ulcers as well as the penetrating ulcers were transformed into chronic ulcerations by this procedure. Lye was utilized in several instances for this purpose, but with less satisfactory results, as the lye would occasion numerous erosions throughout the esophagus while the hydrochloric acid would not affect the normal esophagus but only the area in which the ulcer was situated.

As a result of these experiments, it was demonstrated that active ulceration could be maintained over long periods. In six normal control dogs in which hydrochloric acid was similarly administered, ulceration could not be detected, though occasionally small erosions were observed which were due to the trauma produced by the insertion of the esophagoscope or stomach tube. When large doses of acid were frequently introduced through a tube into the esophagus of a dog, considerable bleeding of the ulcer was observed through the esophagoscope. This bleeding usually occurs as soon as the ulcer has formed and in most instances continues as long as the acid is administered. If the administration of acid is continued over a varying period of time, the animal will usually begin to regurgitate large quantities of blood mixed with mucus. One also observes that the animal loses much weight during this period, notwithstanding the fact that he still continues to consume the usual quantity of food and that he becomes anemic. If the ulcers were allowed to heal and acid was not administered during the intervening period, the further application of acid did not disturb the scar or produce any effect on the esophageal wall.

In the erosion or mucosal type of ulcer, feeding with acid prevents rapid healing, but in the penetrating ulcers the continuous use of acid will frequently produce perforation or healing is markedly retarded. In seven dogs, the mucosa of the esophagus was scarified. In three of these, acid was not administered; these ulcers healed promptly, while in four in which acid was given bleeding ulcers were produced in which healing was greatly delayed. Even in the animals with deep ulcerations healing was prompt when the animal was not treated with acid, while when acid was given perforation was frequently produced. In every instance in which the acid was administered, regardless of whether the ulcer was superficial or deep, the ulcerated area was usually increased in size to an extent dependent on the length of time of the treatment. Lye was administered to two dogs over a period

of two months. Large doses (a half teaspoonful to one teaspoonful of concentrated powder dissolved in 3 ounces [89 cc.] of water) were given twice daily over a period of four weeks. Numerous ulcers were noted during the esophagoscopic examinations, which were performed weekly. These ulcers appeared superficial and bled easily and

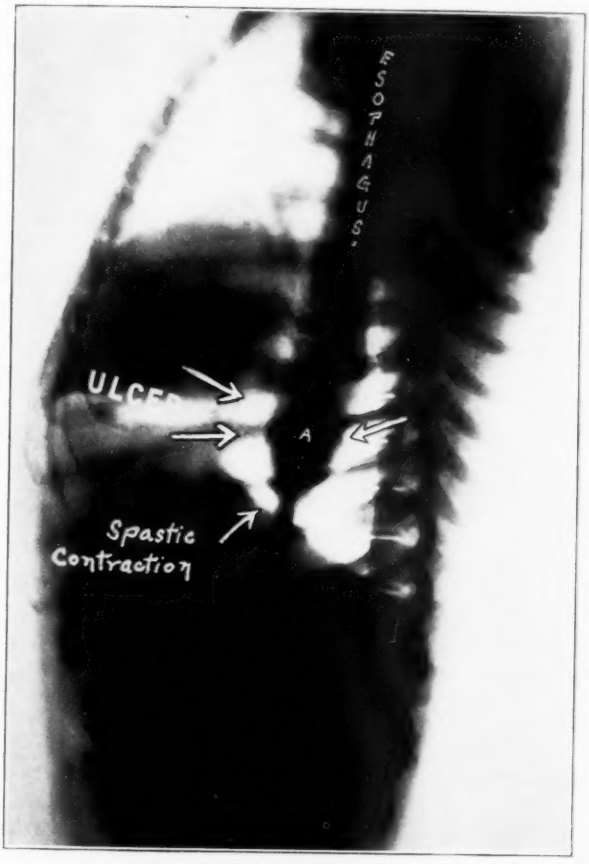


Fig. 1 (dog 13).—A large ulcer crater filled with barium overshadowed by the surrounding esophagus; confirmed by esophagoscopic examination; cardiac end shows typical spastic contraction frequently noted in ulcerations.

freely. However, following discontinuance of the use of the lye healing occurred promptly, and on further examinations the esophagus was found to have assumed a normal appearance in a single instance; while in the others, numerous small pinkish areas were observed which

indicated that the ulcers had almost completely healed. This was verified at autopsy. Bleeding was a persistent and constant sign in all of the active ulcers, though serious hemorrhages were not encountered in this series. Strictures followed by obstruction were not noted. A marked increased secretion of mucus was also observed. It is of great advantage to have roentgen-ray investigations precede esophagospy, as has also been recognized in human beings.

Due to the difficulty encountered in visualizing the esophagus when obstruction does not exist, it is necessary to administer the opaque barium meal in a continuous flow in order to obtain satisfactory roentgenograms. The animal is placed on the abdomen with a special gag in the mouth, and through an opening in the gag the stomach tube is passed

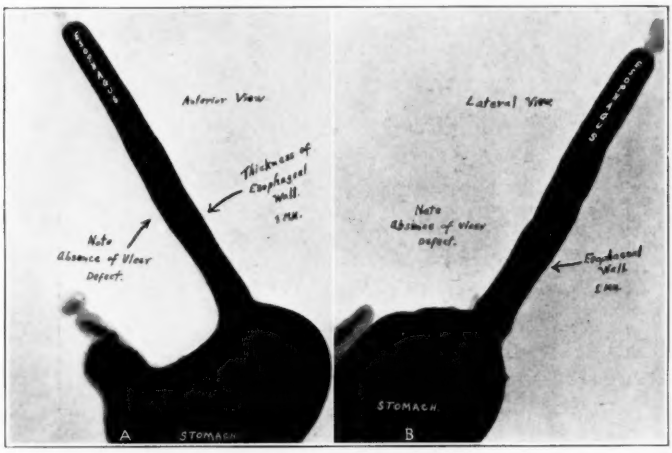


Fig. 2 (dog 13).—*A*, specimen obtained at autopsy. Anterior view. Ulcer allowed to heal. The absence of the filling defect should be noted. The condition was confirmed by esophagoscopic examination and at autopsy. *B*, lateral view.

into the esophagus for about 6 inches (15 cm.) from the teeth. After one is certain that the tube is in the esophagus, it is then attached to another tube which is connected to the barium container; the barium meal is allowed to flow into the esophagus slowly but steadily by means of gravity. During the x-ray examination films are taken in two positions, oblique and postero-anterior. The flow of barium is discontinued, and another film is taken in the oblique position when the esophagus has emptied itself. This is an important procedure.

Experimental ulcers of the esophagus produce essentially three types of filling defects: (1) defects projecting from the esophageal outline; (2) defects partly displacing the esophageal outline, and (3) spastic defects.

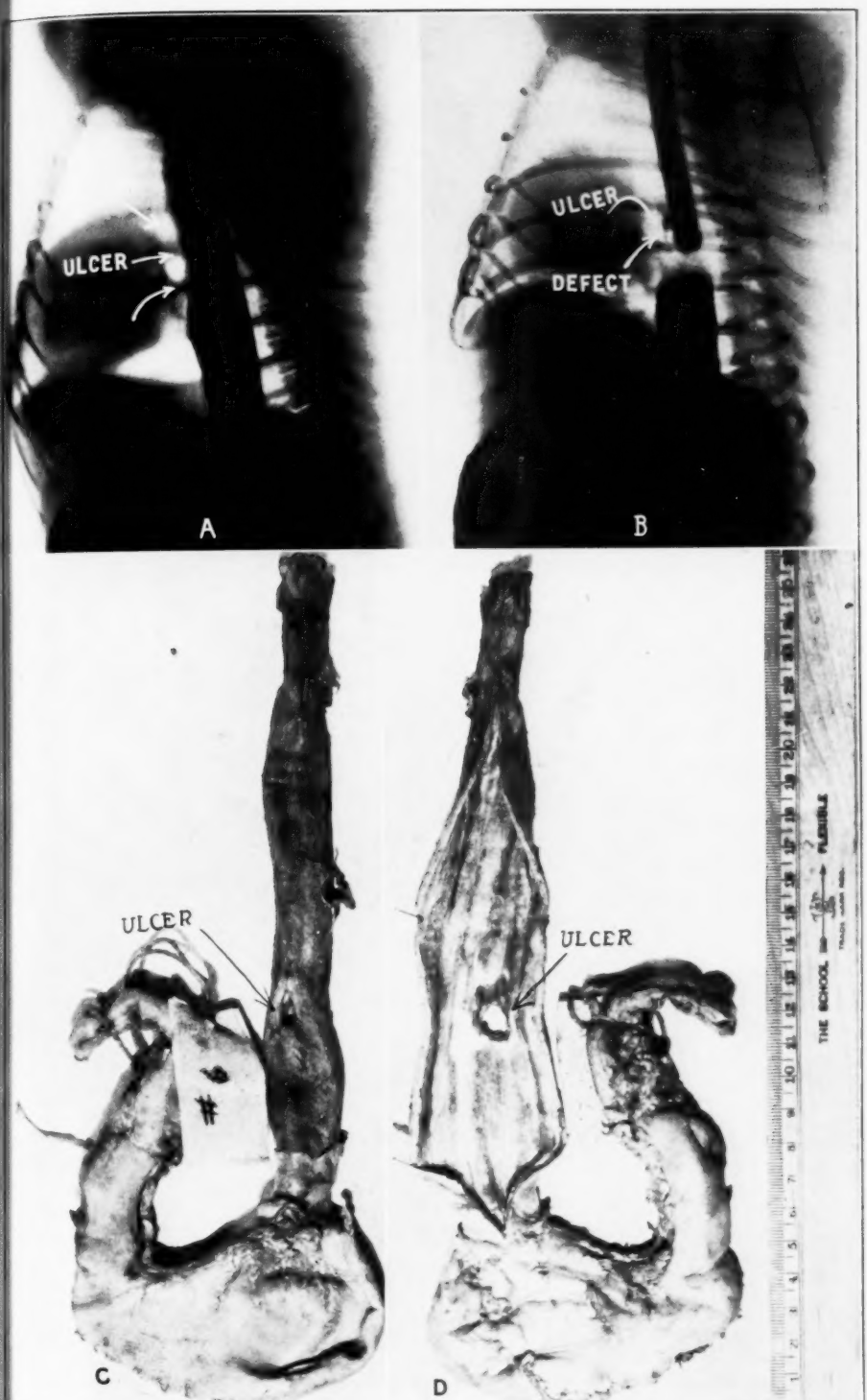
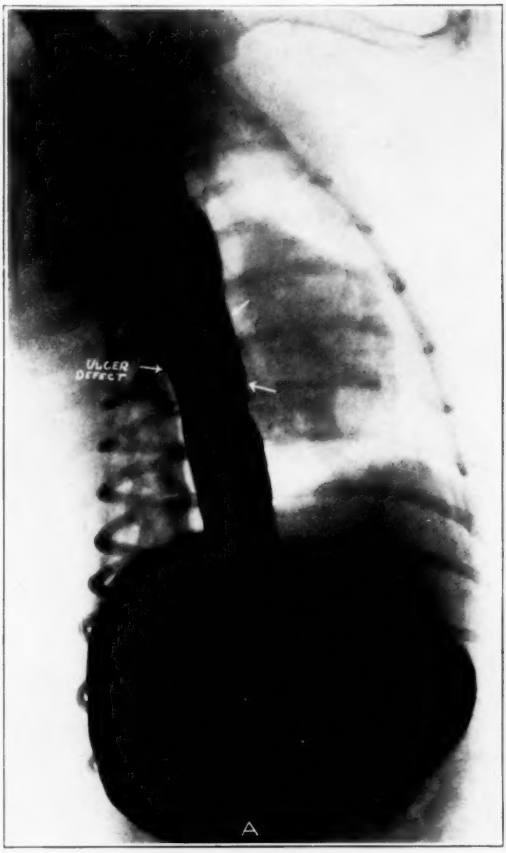


Fig. 3 (dog 6).—*A*, esophagus when filled showed a displacing type of filling defect. This was confirmed by esophagoscopic examination. *B*, the typical ulcer defect of the penetrating type when the esophagus is empty should be noted. *C*, perforation following the administration of 10 per cent hydrochloric acid solution. *D*, shows the size of the perforated ulcer, with the esophagus opened.



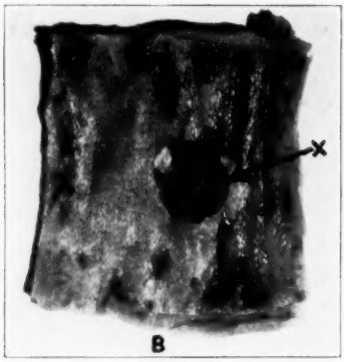


Fig. 4 (dog 12).—*A*, small penetrating ulcer defect on the right posterolateral wall, with slight displacing defect opposite. This was confirmed by esophagoscopic examination. *B*, the dog was killed five days following the administration of 2 drachms of 10 per cent hydrochloric acid solution four times daily. The large punched out ulcer crater should be noted. *X* indicates the ulcer.

The diagnosis of ulcer of the esophagus is made roentgenologically in a manner similar to that observed in gastric ulcer. A persistent filling defect is direct evidence of this condition. However, defects are frequently extremely difficult to demonstrate when present in the esophagus largely due to the location of the ulcer and the position in which

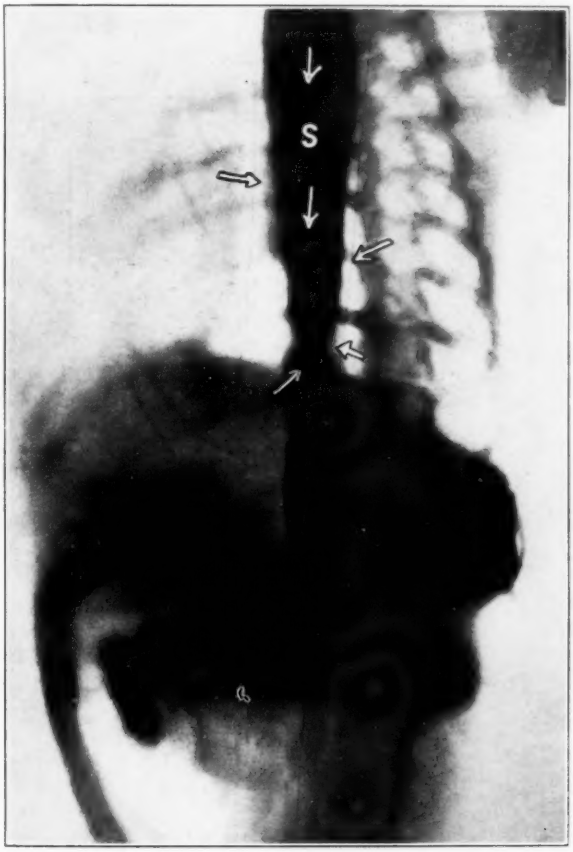


Fig. 5.—The tapering spasm frequently found in ulcer of the esophagus.

the x-ray examinations are made. Filling defects are frequently best observed immediately following the emptying of the esophagus of an opaque meal. The ulcer crater will under these conditions retain sufficient of the barium meal to reveal a shadow varying in extent according to the size of the ulcer. On the other hand, the ulcer will at times

show to best advantage when the esophagus is well filled. This is especially true in those instances in which deep penetrating and perforating ulcers exist.

Mucosal ulcers do not always reveal defects in the roentgen-ray examinations, as the crater is often too shallow, but may in some instances show a small fleck situated in the ulcerated area after the esophagus has emptied. These ulcers, however, frequently present a spasticity which is often characteristic of this type.

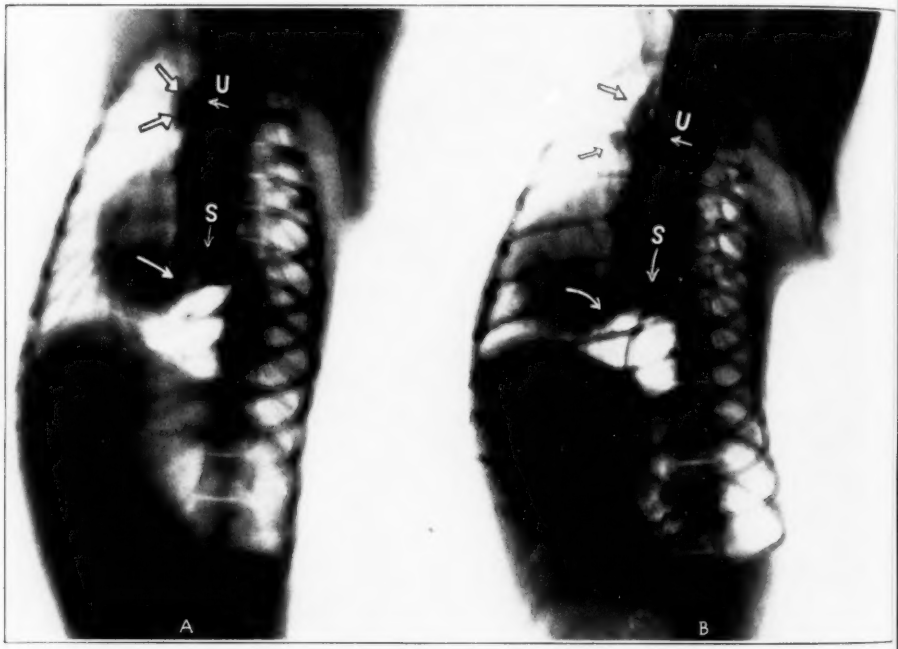


Fig. 6.—*A*, large penetrating ulcer on lateral wall at *U*. *S* shows marked spasticity with signs of obstruction. *B*, same dog, showing perforation.

Penetrating ulcers, when large, frequently simulate diverticula. The defect produced by this form of ulcer is of the projecting type, which is typical and characteristic of this lesion. It is observed as a large regular or irregular shadow when the esophagus is empty, or as a defect or niche when it is filled. Occasionally, a defect will not be observed at first, but if the examination is repeated, it may show subsequently in another position.

On account of the thinness of the wall of the esophagus in dogs, perforation not uncommonly follows as a complication in ulcerations.

Fig. 7.—Esophagoscopic drawing of a chronic ulcer of the esophagus.

The perforating ulcer is also revealed roentgenologically as a projecting type of defect. Spasm of the esophagus is frequent; the characteristic spasm caused by an ulcer is of the tapering type; but at times spasm may be observed which produces a displacing defect opposite the ulcer or in the ulcerated area. Occasionally, spasm may be so marked as completely to cut off the barium meal, giving the appearance in the picture of an organic obstruction. By means of esophagoscopic examinations, these ulcerations were observed directly and their size noted and bleeding detected; a grayish membrane and pinkish white scar were revealed when healing occurred. In the ulcer that has been present a

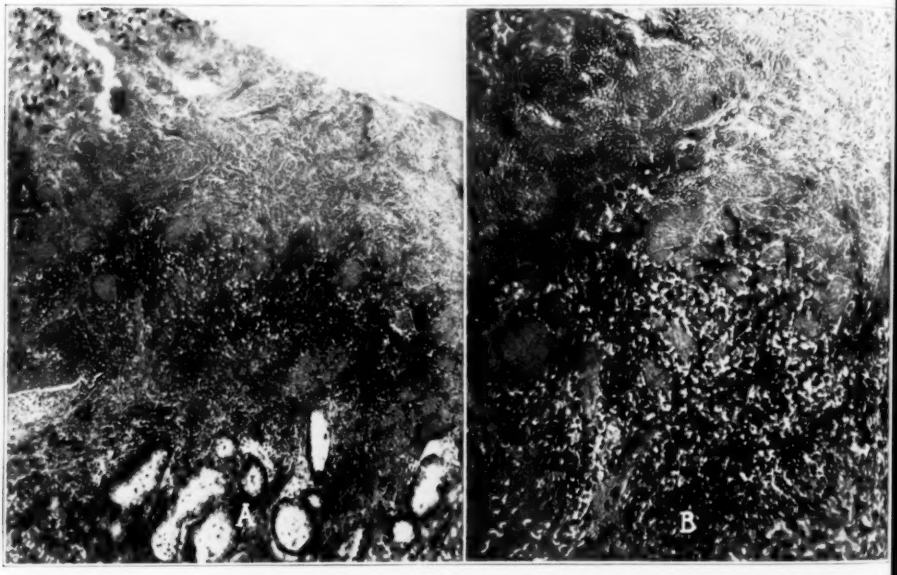


Fig. 8.—*A*, an ulcer undergoing extensive necrosis. Low power magnification. *B*, high power magnification of *A*.

long time, definite induration and thickening were not noted. The ulcer appears well defined, and its edges are sharply outlined and are occasionally everted and irregular. The base of the ulcer appears smooth and is apparently regular. These observations were confirmed by the condition found at autopsy. The ulcers bleed readily when touched with an applicator during the esophagoscopic examination. Fixation of the esophagus, as is occasionally found in the human being, was not noted in these experiments. The esophagoscopic appearance closely resembles ulcers of the peptic type. In this form of ulcer, it is dangerous to remove specimens for pathologic study for fear of producing perforation.

It is interesting to note that diet plays but a slight rôle in the healing of these ulcerations. Even when the animals were fed with bones and tough meat, a change in the appearance of the ulcer could not be detected. When these ulcerations are fully established, the animal exhibits difficulty in swallowing with evidence of pain when food passes over the ulcerated area.

The pathologic appearance of a typical ulcer, as was observed in dog 12, is characteristic. The gross specimen shows a large round ulcer in the lower third of the esophagus on the lateral and posterior aspect, about 8.5 cm. from the cardiac orifice and measuring 12 by 15 mm. and about 2 mm. in depth; the floor of the ulcer is relatively smooth, with a slight sloping toward the center. The edges are cleancut and slightly everted. The mucosa near the ulcer appears normal. The

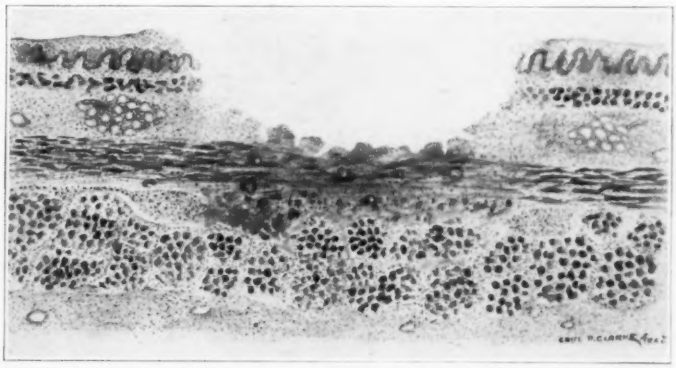


Fig. 9.—Microscopic drawing of a typical ulcer of the esophagus.

ulcer has the appearance of a peptic ulcer such as is observed in the stomach and duodenum.

Sections of the esophagus present the ulcer extending into the inner circular muscular layer and in its deeper portion involving the adjacent muscle bundles. Toward the edges, the ulcer does not extend any deeper than the submucous layer. The floor of the ulcer is covered with fibrin and pink staining necrotic tissue. Throughout this area and in the adjacent living tissue, there is a moderate diffuse leukocytic infiltration. The outer fibrous coat and the muscular coats are edematous and show a moderate leukocytic infiltration. The blood vessels at the base of the ulcer are dilated and contain red blood corpuscles. Leukocytic margination is observed. Similar though less marked vascular changes are noted in the more remote tissues. A number of the smaller arteries and capillaries in the tissue beneath the floor of the ulcer contain

hyaline thrombi. The stratified squamous epithelium (mucosa) ends abruptly at the edge of the ulcer; beyond this point on either side, it appears normal. The submucous glands beyond the area of ulceration are normal.

CONCLUSIONS

1. Ulcers of the esophagus produced by removal of a small section of the wall through the esophagoscope will heal readily within a week.

2. Ulcers when treated with a 10 per cent solution of hydrochloric acid will become chronic, and healing will be markedly retarded.

3. Perforation is a frequent occurrence when deep penetrating ulcers are treated with acid.

4. Ulcers when uncomplicated do not form strictures but heal readily.

5. The x-ray examination reveals defects and spasm in most instances, which are characteristic of ulceration.

6. Large penetrating ulcers may simulate diverticula.

7. The ulcer is clearly demonstrated on esophagoscopic examination.

PALM COLOR TEST

A SIMPLE, PRACTICAL CLINICAL METHOD FOR THE DIAGNOSIS OF ANEMIA AND PLETHORA

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I shall describe in this paper a simple, practical clinical test which is useful in the diagnosis of anemia and plethora, and which is accurate and dependable in the hands of those who are well acquainted with it. In fact, I believe, it is one of the most accurate and dependable methods of detecting slight grades of anemia or plethora. Through its use, one can detect a gain or loss of 200 cc. of blood given by transfusion or withdrawn by venous section.

In the earlier days of medical science, a diagnosis of anemia or plethora depended on examination of a patient's color, or the color of a freshly drawn specimen of blood. In more recent years, laboratory estimations of the red count and percentage of hemoglobin have gained precedence over this simple practical method of examination. Since the introduction of methods of estimating plasma volume and blood volume, there have been additional valuable means of making more accurate the laboratory diagnosis of anemia and plethora. With many physicians, the use of one or several laboratory methods has completely supplanted the common sense observation of a patient's color. This is unfortunate, for laboratory examinations, per se, occasionally lead to gross and often unfortunate error in judgment, both in diagnosis and treatment. Furthermore, laboratory methods are rather complex and are not at the disposal of the profession at large. Finally, laboratory tests are not always at the disposal of the relatively few who are sufficiently practiced to make them and interpret the results correctly.

The commonly used blood counts and hemoglobin estimations do not tell the whole story concerning the presence or absence of anemia or plethora because of the fact that an important factor still remains unknown, namely, blood volume. It is a well known fact that a patient with a normal red count and percentage of hemoglobin may be anemic or plethoric because of an abnormal blood volume. At the present time, there is available to the profession an ingenious method of estimating plasma volume and blood volume. Results of this combined with red counts and hemoglobin estimations might deceive one into believing that these results can be used infallibly in the diagnosis of anemia and plethora. This happy state of affairs does not exist at the present time, for even with these results obtained with flawless technic, there is still an important

unknown quantity which prevents their use without limitation in diagnosis; one remains at a loss to know whether or not the results actually found are the optimum for the patient under observation, or whether they are too high or too low. One is confronted with the same obstacle that is presented in basal metabolic estimations if it is impossible for some reason to calculate theoretically the normal rate of oxygen consumption for the patient under observation and for this reason one is unable to decide whether the results actually found in the patient are normal or abnormal.

There are at the present time relatively accurate methods for estimating blood volume for given persons. There is no infallible method, however, for calculating theoretically what the blood volume for the person ought to be and, therefore, one may be at a loss to know whether or not the result found is the optimum for the patient. This state of affairs should seem self-evident to those who will bear in mind that some persons are muscular and active and naturally demand a greater blood volume per unit of weight than fat phlegmatic persons with small muscles and small internal organs. A volume of blood which would be normal for an athlete such as a professional wrestler would naturally be too great for a patient with hypopituitary obesity, who might have the same height and weight. It is self-evident that fatty tissues contain less blood per unit of weight than active muscle tissues and much less than the internal organs such as the spleen, liver, and finally the heart and large blood vessels. Greater difficulties are encountered under certain pathologic conditions in which the capacity of the vascular system is increased or reduced by cardiac or vascular anomalies, aneurysms, malignant conditions, pregnancy, and other conditions, and on this account, the blood volume optimum per unit of weight is made unusually great or small. If one has an accurately determined red count and percentage of hemoglobin, therefore, and an accurately determined blood volume, one still lacks in many cases, the information which is desired most of all, namely—a knowledge as to whether the patient has exactly what he needs in the way of a total quantity of circulating hemoglobin.

These are not the only difficulties to be encountered under pathologic conditions. It was pointed out by Dr. D. D. Stofer and myself [1] a number of years ago, that in one of the most important and most common forms of anemia, namely, pernicious anemia, there is a state of affairs which makes all methods of examination go awry. This state of affairs consists of a marked difference between capillary and venous red counts. I found that the capillary blood count is always much higher than the venous blood count in pernicious anemia, and that in the average case this difference amounts to as much as from 500,000 to 1,000,000 cells or more per cubic millimeter of blood. This difference in the case

1. Duke, W. W., and Stofer, D. D.: A Comparison of Capillary and Venous Blood in Pernicious Anemia, Arch. Int. Med. **30**:94 (July) 1922.

of severe anemia is gross indeed, in fact, it is not uncommon to find a capillary count more than 50 per cent greater than the venous count. Red counts, hemoglobin estimations and blood volume methods used in this disease, therefore, give a false idea concerning the actual status of the volume of circulating hemoglobin.

One may as well admit frankly, therefore, that in studying anemia, variables and obstacles are encountered which, under certain conditions, seem discouragingly gross. This and the foregoing statements are not made for the purpose of throwing discredit on present day laboratory methods; they are made rather for the purpose of pointing out that laboratory methods at best have their shortcomings. They actually

Fig. 1.—Note a marked difference in color between the two hands of normal persons because of difference in position. A difference as marked as this between the color of a patient's hand and the control would indicate a large difference in the mass of circulating hemoglobin (from 3 to 4 points of normal blood) if the test was made as described in the text. The photograph illustrates how little can be gained by examination of the skin of the face, the lips or the conjunctivae if the posture of the patient is not taken into account. When the patient is in a lying posture the face surfaces are more highly colored than in an erect posture. If the face is below the level of the base of the heart, the degree of redness becomes still more marked.

equal, I believe, or possibly exceed the shortcomings of the color test to be described, which is so simple that it can be used by any physician who has what is commonly known as horse sense.

It is a time honored custom for physicians to diagnose anemia or plethora by observing a patient's color, that is, by observing the color of

the face, lips, conjunctivae or nails. That this method of diagnosis is inaccurate should seem self-evident. A moment's observation of the faces of one's friends should immediately disclose the fact that of persons who believe they are normal, some have red faces, others pale faces, some red lips, others pale lips, some rosy ears and others pale ones. Even the color of the nails and back of the hands varies greatly in normal persons. Furthermore, the color of a person at different times in the day will vary grossly in these localities. The face, an organ of expression, is subject to marked variation in color under the influence of many factors, such as the emotions, change in external temperature or exercise. The color of the skin generally varies greatly with temperature and exercise because of the function of the skin in regulating the loss of body heat. A physician, therefore, cannot gain reliable information concerning an abnormality in the blood by observing the color of these parts unless the change is marked indeed. The conjunctivae, a time honored location for the observation of color, are also subject to variation under conditions other than those due to change in the total quantity of blood. The color changes, for example, if a patient changes from a sitting to a lying posture. The importance of this variable factor can be seen in figure 1 in which the color of the hands can be compared, one of which is about 1 foot (30.4 cm.) higher than the other.[2] The conjunctivae, with a change from sitting to lying posture, vary owing to the fact that in the erect posture, the vessels of the head tend to be emptied by a column of blood under negative pressure. This gives rise to a difference in color which is marked, indeed, and which is never taken into account by clinicians. So great a difference in two patients in the same posture might indicate a marked pathologic process. When anemia is marked, pallor of the conjunctivae can be observed with definiteness. When plethora is marked, a tinging of the sclerae with pink becomes evident and practically always indicates a serious pathologic increase in blood volume unless accounted for by a local pathologic change. These changes in the conjunctivae can be observed definitely when caused by gross pathologic changes in the blood,

2. It is extremely difficult to photograph color accurately even under ultraviolet light. A slight change in the slant of the hand casts a shadow which appears as darkness and could be interpreted as color. In all the illustrations, an effort has been made to photograph the hands satisfactorily and to show their color in the various stages at which blood volume has been increased or reduced by transfusion or venous section, as the case may have been. When photographs were taken, red counts and hemoglobin estimations were usually made. Unfortunately, in the great majority of cases the color photographed did not give a true picture of the color observed. The photographs which are shown are only illustrative figures which approximate the changes in color. They do not faithfully record events as they actually occurred, and in many instances red counts and hemoglobin estimations were not adequately made at the time the photographs were taken.

but cannot be observed with accuracy nor definiteness when the pathologic change is slight but yet important. The diagnosis of anemia or plethora from the color of the face and conjunctivae are unsatisfactory and inaccurate for another reason; namely, because of the fact that the color is not easily compared with a standard. The color of a patient is usually compared instead with the physician's idea of normal color. Here, personal equation is of necessity a source of gross error. One's own idea of normal color changes from time to time, in fact, to a surprising extent from day to day. This crude method stands in marked contrast with the nicety with which blood volume is regulated by nature in a healthy person. It has properly been nearly supplanted by laboratory examinations, in a struggle for accurate standards.

Hemoglobin estimations of a sample of blood are made at the present time by comparing the color of a patient's blood directly or indirectly with the color of an average specimen of normal blood, that is, by a colorimetric method and by a standard which amounts to nothing more nor less than an average found in normal persons. This method is accepted as fair. The method of testing color to be described is likewise a colorimetric method, but in vivo instead of in vitro. It depends on a comparison of the patient's color with the color of the average normal person. It would seem on first thought that this could be accomplished by examination of any of the surface tissues. This, however, is not the case for, as previously mentioned, most tissue surfaces vary in color under many conditions other than those caused by anemia or plethora.

There exists one skin surface in which color varies remarkably little unless a person is anemic or plethoric, and from its color an idea can be gained concerning the quantity of hemoglobin which is actually in the general circulation. This surface is the palm of the hand.

The palm of the hand is meant for work. It is not an organ of expression, subject to marked normal variation in color like the face, nor is it a surface designed, I believe, to help to any marked extent in regulating the loss of body heat as is the skin surface generally. Furthermore, it is not often exposed to direct sunlight, so consequently its color is not influenced much through this agency. For these reasons, marked and frequent constriction or dilatation of the vessels of the palm would seem less purposeful physiologically than for vessels of other surfaces of the skin. Practically it is not often marked—at least under conditions under which a patient sees a physician in his office, home or in hospital practice. This statement is based on thousands of observations that I have made during a period exceeding ten years. The color of the palm of the hand is remarkably constant under the usual normal conditions of living. The palm of my own hand compared repeatedly with those of several assistants from time to time is always exactly the same.

METHOD

If a physician's palm is normal in color, it can be compared with the patient's, and slight differences in color can be estimated with accuracy. This is true whether the patient examined is a day laborer with calloused palms, or a woman with thin skin, or a child. It can frequently be made with relative accuracy even in pigmented races, such as the Indians. In many of the pigmented races, the palm of the hand is pigmented less than the skin generally, and often little at all. Furthermore, the estimations can usually be made whether a patient is sick or well, emotionally upset or otherwise. Relatively few physiologic conditions and few illnesses, other than anemia or plethora, change

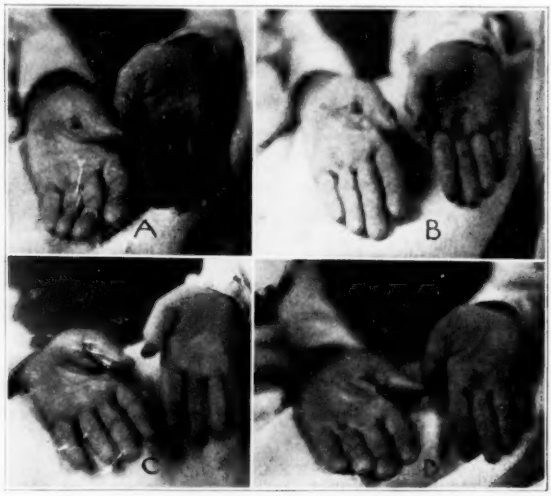

Fig. 2.—In *A*, the palm on the left is that of a man weighing 220 pounds (99.7 Kg.) who had a severe acute hemorrhage from the gastro-intestinal tract. The red count was 2,880,000; the hemoglobin, 50 per cent. The palm of the hand appeared almost bloodless. The illustrations (taken by daylight) reproduce poorly the enormous changes in color which were actually observed. *B* indicates the palm after the introduction of 1,340 cc. of blood by direct transfusion from two large plethoric donors; the red cell count was 3,624,000; the hemoglobin, 65 per cent. *C* shows the palm after the introduction of an additional 1,200 cc. of blood by direct transfusion from two donors; red count, 4,168,000; hemoglobin, 80 per cent; normal color not completely established, and *D*, after a lapse of two weeks; the red cell count was 4,320,000; the hemoglobin, 80 per cent. Color was not completely re-established in this patient because of the fact that he was plethoric prior to his hemorrhage with a red count of 6,560,000. It was assumed that he would soon re-establish normal color, if not an increased color, without further addition by transfusion. At a later date he was bled because of recurrence of policythemia.

the color of the palm in marked degree. Several important exceptions will be mentioned subsequently. Additional exceptions may be discovered in the course of time.

The technic of comparing a physician's palm with that of a patient would seem simple. The fact is, however, that it is not simple, and unless the comparison is made accurately and in a definite way, it will prove grossly misleading.

In the first place, one must know whether or not the physician's palm is normal. This can be determined by comparing the physician's palm with that of many young healthy adults. If the physician's palm proves normal in color it can be used as a standard for comparison with patients. Otherwise, it cannot be used, and some other person must be chosen for a standard.

When the comparison is made, both patient and physician should either stand or sit comfortably. The hand of each should be semiflexed and should be held at about the level of the apex of the heart, or a little above for a few moments, until constant permanent color has been established. It is essential that the distance between the hand and the base of the heart be identical in both physician and patient, and that in neither should the skin of the palm be stretched. One can convince himself of the importance of these two statements if he will compare his own palms, one hand semiflexed and the other markedly extended, and if he will raise one hand above the level of the other for a moment and then compare the color of the two. This makes a gross difference almost immediately. Interesting red and white spots, should they appear, can be eliminated if both the hand of the patient and standard are held at a slightly higher level.

If these details are attended to, the color of the patient's palm can be compared with the physician's standard. Under the usual normal conditions, the color of both patient and physician will be practically identical as to both fingertips and palm. If the patient is slightly anemic, his plan will be paler than the physician's; the fingertips may appear the same. If the patient is anemic (secondary anemia) to such an extent that the red count or percentage of hemoglobin is definitely reduced, the difference in color between the patient's hand and the physician's will be so striking that it could not possibly be overlooked. The patient's fingertips and palms will both look pale, by comparison. If anemia is of such a grade that the red count lies much below four million, the patient's palm will look almost bloodless as compared with the physician's (exceptions to be mentioned subsequently). If the patient is plethoric, the change is equally striking. If he is plethoric to such an extent that the blood count or percentage of hemoglobin is definitely increased, the abnormal redness will be so marked that it could not possibly be overlooked.

With practice in the use of this method, a physician can become so expert that by making this comparison in color, and noting the size and muscular development of a patient, he can predict with relatively small error the quantity of blood which will be required by transfusion to re-establish normal color in an anemic person. He can likewise, though with less accuracy, predict in plethoric persons the quantity of blood which will have to be removed by venous section to establish normal color. He can, furthermore, tell with relative accuracy when an optimum quantity of blood has been given during transfusion, and when the transfusion should be stopped. These statements are based on a broad clinical experience in which the test has been used thousands of times and compared with clinical and laboratory observations and with the results of transfusion in anemic patients and venous section in plethoric patients. It has been used as a guide during more than 1,000 direct transfusions of blood and has proved dependable and useful.

EXCEPTIONS TO THE RULE

Relatively few common conditions other than anemia or plethora change the color of the palm in a person indoors and at rest. Red and white spots, if present, may interfere with the accuracy of the test; this difficulty can be overcome by elevating the hands a little. Cyanosis, or jaundice, if marked, may seriously interfere. Patients with Renaud's and other diseases of the arteries or veins, with chilblains, and patients whose hands have been scalded, or kept in hot water a great deal, usually have abnormal palms as the result of local conditions in the extremities, and in these the test cannot be made with accuracy. Furthermore, in patients with certain diseases of the skin, in patients in syncope or shock and in a few patients with goiter, the test is not accurate. Furthermore, I have gained the impression that the Latin races and persons living in hot climates under normal conditions tend to have more highly colored palms than the average person in this district. Furthermore, rather obese persons who are over middle age often show more color than usual. This may be pathologic, or may be a compensation to increase surface cooling in the obese; on the other hand, it may indicate a mildly pathologic condition which needs correction in the same sense that obesity indicates the desirability of correction. Finally, in some forms of anemia, namely, pernicious anemia, one encounters the unusual factor which has been mentioned, namely, a tendency for the corpuscles, especially the macrocytes, to lag in the skin capillaries. As previously mentioned, the capillary count in patients with pernicious anemia who have not been treated is always greater than the venous blood count and is often more than 50 per cent greater. This condition gives rise to an unusually rosy color in the superficial tissues in patients with pernicious anemia, even when the capillary red count is reduced by one

or two million or more. In fact, a patient with pernicious anemia who has a capillary red count as low as three million, with the venous count much lower, may have normal or increased color both in the palms and in other surfaces. In pernicious anemia, therefore, one cannot interpret color according to the same rules as one does in persons with secondary anemia. In fact, in cases of pernicious anemia in which treatment

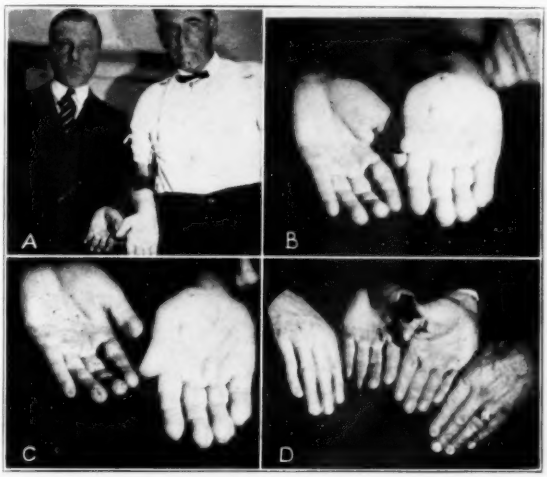

Fig. 3.—In *A*, the man on the right has a severe case of pernicious anemia; he weighs considerably over 200 pounds (99.7 Kg.). The photographs were taken by ultraviolet light. Note the marked contrast between the pallor of the palm and the relatively normal color of the face; this is not rare in pernicious anemia. One could hardly detect anemia in this patient by examination of the skin or lips. The conjunctivae were pale and the palm of the hand appeared almost bloodless; the red cell count was 1,420,000; the hemoglobin, 30 per cent. *B* shows the palm after the introduction of 600 cc. of blood by direct transfusion; the red count was 2,170,000. *C* was taken after the introduction of 600 cc. of blood by direct transfusion. Note how little gain in the color of the palm has occurred after the introduction of this amount of blood. The red cell count was 2,860,000. *D* indicates the hands after the introduction of 500 cc. of blood by direct transfusion; the red count was 3,200,000. Note that both the back and palm of the hand approximates normal in the photograph. There was in reality a marked difference between the real color of the palm and the normal which is not shown in the photograph. Note how deceptive a comparison of the backs of the hands may be; the anemic patient shows more color than the normal. An additional 500 cc. of blood was required to restore a satisfactory color. The patient left before complete blood examinations and photographs could be made. Note also that color does not appear after the first transfusions but appears quickly as blood volume approaches normal; this is the rule. In one person (not illustrated), four donors were used before any noteworthy change in the color of the palm was visible. Two donors used subsequently, especially the second one, restored the color of the palm to normal with great rapidity.

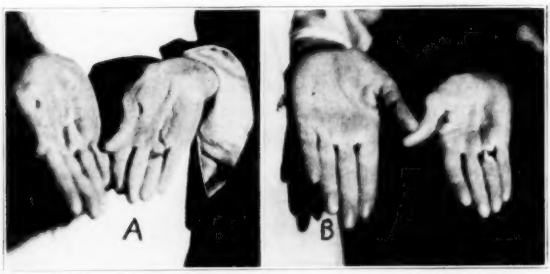

Fig. 4.—*A* shows the palm of a woman with pernicious anemia (on the right); her weight was about 85 pounds (38.6 Kg.). The red count was 1,180,000; the hemoglobin, 50 per cent (taken by sunlight). *B* shows her palm after the introduction of 1,200 cc. of blood; the red cell count was 3,370,000; the hemoglobin, 80 per cent. Note that in spite of the persistent low red cell count, the color was restored to about normal.

The reproductions, especially of this illustration, are not as clear and distinct as might be desired, and do not adequately illustrate the condition under discussion.

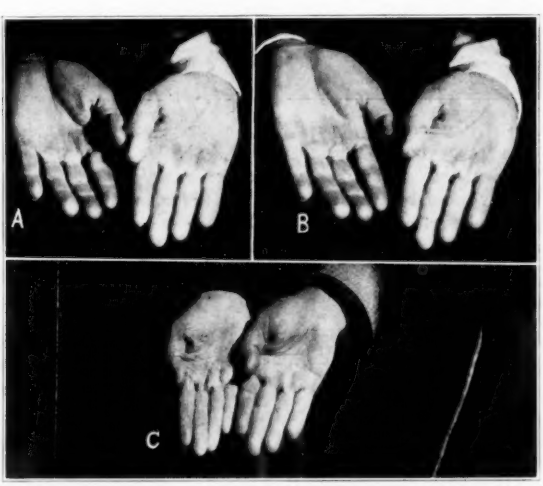

Fig. 5.—*A* shows the palm of a man with secondary anemia (on the right); his weight was 180 pounds (81.6 Kg.); the red cell count, 3,490,000; the hemoglobin, 45 per cent. *B* shows the palm after the introduction of 1,700 cc. of blood from three donors; the red cell count was 4,230,000. *C* indicates the same palm after the introduction of 600 cc. of blood; the red cell count was 5,200,000; the hemoglobin, 80 per cent. The patient was subjectively normal.

has not been given, a red count exceeding three and one half million seems harmful to the patient in the presence of marked macrocytosis. The patient tolerates better a moderately reduced count with palms of normal color or slightly paler than normal. On the Minot and Murphy diet, the status changes. In successfully treated patients, macrocytosis becomes less marked, and capillary and venous counts may then run about parallel.

Fig. 6.—The palm of a man with a case of high grade plethora (right); his weight was in excess of 200 pounds (99.7 Kg.). He gave a past history of having had nosebleed to the extent of from 1½ to 3 pints on four separate occasions, each time with improvement in his general strength and a feeling of well being. A venous section had been performed on one occasion to the extent of 3 pints. He lost 7½ pints a few days later from epistaxis following a nasal operation. He said that following this he never felt better in his entire life. Examination showed a picture of a highly plethoric person with a beefy-red appearance of the palms, as shown in the photograph. In spite of this, however, his red cell count was only 5,300,000 and the hemoglobin, 95 per cent. One pint of blood was withdrawn on each of two consecutive days with a change in the color of the palms to be noted in the figure on the right.

SUMMARY AND CONCLUSIONS

1. A slight or marked grade of either anemia or plethora can be diagnosed most readily, I believe, through a comparison of the color of the palm of the hand of the patient with that of a proved normal person according to a simple technic which has been described.

2. The skin of the palm of the hand was chosen for making this comparison because under the usual conditions indoors, the color of the palm is remarkably constant in a given person. The color of the palm is believed to be more constant than the color of other surfaces, because of the fact that it is believed to take a smaller part in regulating the loss of body heat than other surfaces, and for this reason is not changed to any great extent through the effect of small differences in tempera-

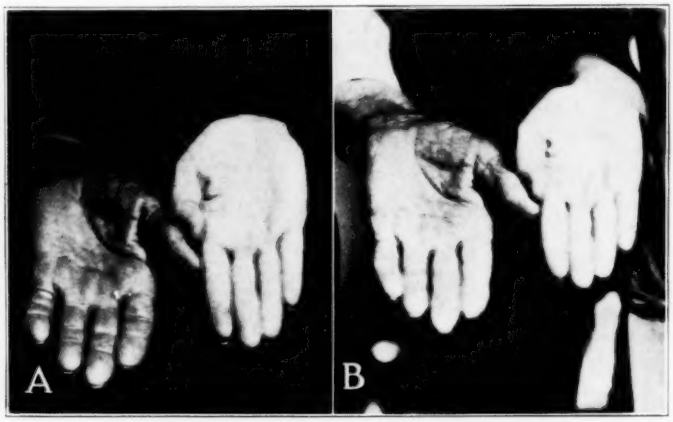

Fig. 7.—In *A* the palm on the left is that of a patient with true polycythemia and a red cell count of nearly 8,000,000. Contrast this with the plethoric person shown in the previous figure who had a red cell count scarcely exceeding 5,000,000. In *B*, note the paling of the palm following the withdrawal of 2,000 cc. of blood in divided doses. The red cell count was eventually reduced to nearly normal with marked improvement in health.

ture and exercise. It, furthermore, does not vary in color through the effect of emotional disturbances as does the skin of the face, nor does it vary in different normal persons to the same extent as does the color of the lips or nails. It seems better adapted, therefore, for the estimation of average color than other skin surfaces. Exceptions to this rule are mentioned in the text.

3. The palm of the hand is preferred, furthermore, because of the fact that if held at the level of the apex of the heart, the color is not modified by changes in the position of the patient. The color of

other surfaces, such as of the face or conjunctivae, is greatly influenced by a change from a standing to a lying posture.

4. I have found after a large experience that the color of the palm is influenced by few conditions except anemia and plethora, and that from a comparison of the patient's palm with that of a normal person, one can demonstrate slight deviations from the optimum in the quantity of hemoglobin in the general circulation.

5. Comparison of the palm of the patient's hand with that of a normal person during and after blood transfusion and during and after venous section is a most reliable guide when one wishes to decide whether or not an adequate amount of blood has been introduced or withdrawn.

5. If the foregoing statements are true, anemia and plethora in slight grade are common conditions.

7. Physicians who study carefully the color of the palm of the hand on a number of patients according to the technic described, and who keep in mind the exceptions mentioned in the text, will find they have a simple, accurate and direct method of examination which can be used fearlessly in diagnosis.

COMMENT

In presenting this paper I hope that my efforts are not misunderstood. I am presenting a method for observing a patient's color, which I think is far more accurate and dependable than methods which have been used prior to this time. I am not presenting a method for the estimation of blood volume or hemoglobin ratios.

I believe, however, that through careful testing of a patient's color one can gain valuable information concerning the status of his blood, that is, whether the total quantity of hemoglobin in circulation is optimum for the patient, or too high or too low. A patient's color does not depend wholly on his blood volume, his red count, the hemoglobin content of a unit of blood, or on the capacity of his vascular system in proportion to his needs. His color depends rather on a mean between all these factors. One gains a result, therefore, in testing color which can be obtained, I believe, in no other way and which is, I believe, an important procedure in studies of anemia and plethora. It gives the same impression that physicians have gained through centuries of time by examination of the color of the conjunctivae, lips, nails and other parts of the body except that it is gained through the use of a method which is evidently much more accurate and dependable.

THE PARATHYROID GLANDS

THEIR RELATIONSHIP TO THE THYROID, WITH SPECIAL REFERENCE TO HYPERTHYROIDISM *

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The purpose of this paper is to discuss some of the literature dealing with the thyroid-parathyroid relationship and to present a few facts obtained by an analysis of over 550 determinations of the serum calcium in cases of disease of the thyroid gland. The work has been undertaken to determine, if possible, whether or not there is an actual antagonism between these two glands, as is believed by many authors. The practical value of such research lies in the fact that if such antagonism does exist, then the use of the active principle of the parathyroid glands, which can now be obtained, should be a useful adjunct in the treatment of patients with hyperthyroidism.

The parathyroid glands were first described by Remak [1] in 1855, and later, by Virchow [2] in 1863. The discovery of the parathyroid glands is rightly ascribed to Ivar Sandström [3] who, in 1880, fully described them, and called attention to their anatomic and histologic significance. They were rediscovered by Gley [4] in 1891. Since the publication of these and other early papers,[5] more than 500 papers dealing with these glands have appeared. A cursory review of the literature suggests the possibility that a functional relationship exists between the thyroid and parathyroid glands.

EMBRYOLOGY

A few of the salient facts in regard to the embryology of these glands should be noted. The parathyroid bodies arise as two separate pairs, superior and inferior. The inferior pair, which finally lies behind the inferior borders of the lateral lobes of the thyroid, arises from the third branchial cleft. The superior pair, which finally lies near or on the central or upper part of the dorsal surfaces of the lateral thyroid lobes, arises from the fourth branchial cleft.

Many authors claim that the thyroid arises in part from two lateral bodies which are outgrowths of the posterior wall of the fourth branchial

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* From the Cleveland Clinic, Cleveland.

1. Remak, R.: Untersuchungen über die Entwickelung des Wirbelthieres **35**:194, 1851.

2. Virchow: Die krankhaften Geschwülste **3**:13, 1863.

3. Sandström, I.: Upsala läkaref. förh. **15**:441, 1880.

4. Gley, E. A.: Compt. rend. Soc. de biol. **3**:843, 1891.

5. Kadyi, A.: Arch. f. Anat. u. Entwcklngsgesch., 1879, p. 312. Madelung, O. W.: Arch. f. klin. Chir. **24**:71, 1879. Millzner, R. J.: Occurrence of Parathyroid on Anterior Surface of Thyroid Gland, J. A. M. A. **88**:1053 (April 2) 1927.

cleft. The majority of authors agree, however, that the origin of the thyroid is solely from a median body at the root of the tongue.

ANATOMY

Gross.—The two pairs of glands mentioned are considered the normal number; yet the so-called accessory parathyroid glands have been recognized for many years. Millzner [6] reported the recognition of parathyroid glands in the human body, on the anterior surface of the thyroid in 12.9 per cent of the 162 specimens which had been removed at thyroidectomy. In the dissections in the clinic, the presence of parathyroid glands has been noted frequently. The number of cases in which this condition has been seen is not large enough to justify a statement as to the percentage of incidence, but it is thought that it occurs frequently because of the deformity of the lateral lobes in cases of adenoma.

The size of the parathyroid glands varies greatly, the glands ordinarily being small flattened ovoid bodies lying in the areolar tissue on the surface of the thyroid gland, which measure from 3 to 14 mm. in length and from 1 to 3 mm. in breadth and thickness.

The cut surface of the glands varies from a yellowish or a grayish-brown to a cocoa color.

The blood supply of the parathyroid glands is derived for the most part from the inferior thyroid artery. Many glands, lying on the capsule of the thyroid, especially those on the anterior surface, are directly connected with the thyroid capsule by at least one distinct vessel; moreover, according to the statement of Sacerdoti,[7] the nerve supply is also furnished by the nerves of the thyroid gland. Anderson [8] found that after these nerves pass through the parathyroid capsule, they terminate within the epithelium of each glandule.

Microscopic.—Each gland possesses a capsule of fibrous connective tissue which sends branches into the gland substance, carrying the blood vessels and dividing the parenchyma into bands and clumps of cells of two main types: (*a*) the chief cells, which are large polygonal cells, characterized by a clear cytoplasm and faintly staining nucleus; and (*b*) the oxyphil cells, which are much less numerous. The cytoplasm of these cells stains strongly with eosin, and the nucleus, with hematoxylin.

A so-called "frothy" cell has also been described. Small irregular vesicles which may or may not contain colloid are frequently seen.

Comparative.—Parathyroid glands have been recognized in all classes of vertebrates with the exception of fishes.[9] A failure to recognize the

6. Millzner, footnote 5 (third reference).

7. Sacerdoti: Internat. Monatschr. f. Anat. u. Physiol. **11**:326, 1894.

8. Anderson, O. A.: Arch. f. Anat. u. Entwcklngsgesch., 1894, p. 225.

9. Cowdry, E. V., in Barker, L.: Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, vol. 5, p. 501.

importance of the anatomic arrangement of these glands in mammals affords an explanation for many of the contradictory results obtained by many of the earlier investigators in this field. In the dog and the cat, the parathyroid and thyroid glands are so closely associated that all the parathyroid glands are removed at thyroidectomy, whereas in the rabbit only the superior, or so-called internal pair, are removed. It is interesting to note that although these glands are usually histologically distinct, the association may be so close that it is difficult to know whether the structure is the thyroid or parathyroid gland. Ochsner and Thompson [10] stated that in some birds the parathyroid tissue is directly continuous with the thyroid, not even being separated from it by a septum but forming a single gland, while in others, the anatomic thyroid is entirely like the parathyroid in microscopic appearance.

EXTIRPATION EXPERIMENTS

Hypertrophy of One Set of Parathyroid Glands After Removal of Another Set.—Walbaum,[11] Erdheim [12] and Pepere [13] failed to observe an appreciable increase in the size of the internal parathyroid glands in rabbits after removal of the external glands, although it has since been shown by Haberfeld and Schilder [14] that there is a marked degree of hypertrophy of the internal parathyroid glands in these animals, if, in addition to the external parathyroids, the accessory glands situated on or about the thymus are also removed.

Hypertrophy of the Parathyroid Glands After Thyroidectomy.—Gley [4] held at first that the parathyroid bodies are made up of embryonal thyroid tissue and that they assume the function of the thyroid gland after that organ has been removed. This view has not been substantiated; on the contrary, Gley himself, in association with Nicolas,[15] repeated his experiments and was forced to abandon this view.

Vincent and Jolly [16] have described structural changes in the parathyroid glands of cats following thyroidectomy. Their experiments, however, have never been substantiated.

In many cases, Biedl [17] found that the removal of the thyroid together with the parathyroid interna is almost always associated with hyper-

10. Ochsner, A. J., and Thompson, R. L.: The Surgery and Pathology of the Thyroid and Parathyroid Glands, 1910, p. 226.

11. Walbaum: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:298, 1903.

12. Erdheim, J.: Beitr. z. path. Anat. u. z. allg. Pathol. **33**:158, 1903.

13. Pepere, A.: Arch. de méd. expér. et d'anat. path. **20**:21, 1908.

14. Haberfeld, W., and Schilder, C.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, vol. 29.

15. Gley, E., and Nicolas, A.: Compt. rend. Soc. de biol., 1895, p. 216.

16. Vincent, S., and Jolly, W. A.: J. Anat. & Physiol., 1895, vol. 32.

17. Biedl, A.: The Internal Secretory Organs, London, John Bale, Sons and Danielsson, 1913, p. 52.

trophy of the parathyroid externa, the amount of hypertrophy bearing a direct relation to the length of time after operation. The parathyroid glands of a growing dog one year after thyroidectomy were found to be twice as large as those of controls of the same litter.

Hypertrophy of the Thyroid After Parathyroidectomy.—Hypertrophy of the thyroid following parathyroidectomy has been reported by Edmunds,[18] Lusena,[19] Vassale and Generali,[20] Halpenny and Thompson [21] and others. These experiments seem to support strongly the possibility of a functional antagonism between these glands.

THE EFFECT OF FEEDING THYROID EXTRACT ON THE FUNCTION OF THE PARATHYROID GLANDS

In her experiments on the thyroid, Kunde [22] noted that the administration of thyroid extract exerted a definite influence on the control of tetany in a thyroparathyroidectomized dog in a tetanoid state. In the case of a dog which had previously required from 1 to 1.3 Gm. of calcium lactate per kilogram of body weight per day for the control of tetany, the calcium was discontinued on the eleventh day during the time of thyroid extract feeding, when signs of hyperthyroidism were present. During the following three months, the administration of thyroid extract was continued and there was no recurrence of tetany. The author fails to state, however, whether or not the tetany could be made to recur by the discontinuance of the thyroid extract.

The beneficial results obtained by the administration of thyroid extract to animals with tetany has been observed by other authors, and it is generally conceded that animals with tetany die in a shorter time when they are not given thyroid extract.

Kocher formerly used large doses of thyroid extract and iodothyrin in cases of postoperative tetany, apparently with beneficial results. For many years, Crile has used thyroid extract together with parathyroid extract in the treatment of subjects with postoperative tetany. It must be noted, however, that in these cases there was a coexisting disturbance in the function of both the thyroid and parathyroid glands.

It is interesting to note in this connection that Cameron and Carmichael caused deaths from tetany by feeding thyroid extract to rats. They did not consider, however, that this was a true parathyroid tetany, but that death was probably due to tetany caused by hyperpnea.

18. Edmunds, W.: J. Path & Bact. **12**:101, 1907-1908.
19. Lusena, G.: Studio critica experimentale, 1899.
20. Vassale, G., and Generali, F.: Arch. ital. de biol. **33**:154, 1900.
21. Halpenny, J., and Thompson, F. D.: Anat. Anz. **34**:376, 1909.
22. Kunde, Margaret M.: Am. J. Physiol. **82**:195 (Sept.) 1927.

In this connection, a case cited by Percival and Stewart [23] is interesting. A cretin, in whom the serum calcium was 9.9 mg. per hundred cubic centimeters, was fed thyroid extract. The basal metabolism rose from — 5 to + 37 per cent in three days, the serum calcium remaining 9.9 mg. In twenty-four days, the basal metabolism had risen to 79 per cent and the serum calcium was 13.2 mg. Withdrawal of thyroid extract for fourteen days was accompanied by a fall in serum calcium to 9.6 mg.

THE EFFECT OF THE ADMINISTRATION OF PARATHYROID EXTRACT ON THE FUNCTION OF THE THYROID GLAND

Moussu [24] found that the administration of parathyroid extract to horses had an unfavorable action in cases of myxedema, but was beneficial in cases of hyperthyroidism. He concluded that the hyperfunction of the thyroid was restrained by the parathyroids.

Mandelstamm [25] reported the production of exophthalmos in rabbits by injections of parathyroid extract, an observation entirely contradictory to the work of Moussu. Mandelstamm expressed the opinion that the exophthalmos is due to increase in the activity of the thyroid gland. This conception is strengthened by Kunde's [22] observation that it is possible to produce marked exophthalmos in rabbits by administering thyroid extract.

It must not be forgotten, however, that previous to the isolation of the active principle of the parathyroid glands by Collip, the administration of parathyroid extract had never been on a satisfactory basis. Clinically, however, I believe that parathyroid extract has a weak though definitely positive effect.

THE STRUCTURE OF THE THYROID AFTER ADMINISTRATION OF PARATHYROID EXTRACT AND OF THE PARATHYROID GLANDS IN HYPERTHYROIDISM

Large doses of parathyroid extract have been given to rats by Cameron and Carmichael [26] who failed to observe any consequent changes in the thyroid gland.

Kurokawa [27] produced hyperparathyroidism in 180 rats by transplantation of parathyroid glands. In forty-eight patients in whom the glands were proved microscopically to have remained alive, there were generalized atrophic changes in body tissues, the thyroid being no exception.

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23. Percival, G. H., and Stewart, C. P.: Quart. J. Med. **19**:235 (April) 1926.
24. Moussu, G.: Compt. rend. Soc. de biol. **6**:242, 1899.
25. Mandelstamm, M.: Ztschr. f. d. ges. exper. Med. **35**:370, 1923.
26. Cameron, A. T., and Carmichael, J.: Am. J. Physiol. **58**:1 (Nov.) 1921.
27. Kurokawa, K.: Japanese M. World **5**:241, 1925.

MacCallum [28] reported the structure of the parathyroid glands in cases of hyperthyroidism. He noted several changes but, in general, the parathyroid tissue was said to be normal. Benjamins [29] reported a similar observation. Structural changes, such as the increase of intraglandular connective tissue or the formation of glandlike hollows filled with colloid, have been reported in cases of hyperthyroidism. Kurokawa,[27] who studied the structure of 815 parathyroid glands in many conditions, found that these changes were frequent; however, he did not report the structure in any cases of hyperthyroidism.

I have made a microscopic study of fourteen parathyroid glands in cases of hyperthyroidism. Three of the specimens were from three patients who died from acute hyperthyroidism. In two of the cases operation had not been performed, and in one acute case hyperthyroidism developed one month after the ligation of the superior thyroid arteries. Observation did not reveal any constant change in these glands.

TETANY AND ENDEMIC GOITER

McCarrison [30] stated that in certain parts of India the mothers of cretins and of children born with goiter commonly suffer from tetany during pregnancy. A case has been cited in which tetany developed during pregnancy in a woman with goiter who lived in a district in which endemic goiter was common. When the patient moved to a nongoitrous district, the tetany disappeared, reappearing again, however, after she had returned to the former locality.

THE FUNCTION OF THE PARATHYROID GLANDS AND A METHOD OF MEASURING IT

Ever since it has been known that the extirpation of the parathyroid glands is associated with tetany, much of the study of the function of the parathyroid glands has centered about experimental tetany. This condition has been produced by many methods besides parathyroidectomy, among which are the following: (1) voluntary hyperpnea;[31] (2) precipitation of calcium in the tissues;[32] (3) the intravenous administration of large doses of sodium chloride;[33] (4) intravenous administration of sodium bicarbonate;[34] (5) intravenous administration of neutral or

28. MacCallum, W. G.: Brit. M. J. **2**:1282, 1906.
29. Benjamins, C. E.: Beitr. z. path. Anat. u. z. allg. Pathol. **31**:143, 1902.
30. McCarrison, R.: Lancet **1**:817, 1913.
31. Collip, J. B., and Backus, P. L.: Am. J. Physiol. **51**:568 (April) 1920.
32. Loeb, J.: Am. J. Physiol. **5**:362, 1901.
33. Greenwald, I.: Am. J. Physiol. **28**:103, 1911.
34. Harrop, G. A.: Bull. Johns Hopkins Hosp. **30**:62 (March) 1919.

alkaline phosphates,[35] and (6) the administration of guanidine or the more toxic methyl-guanidine.[36]

A great deal of confusion has arisen as to the actual cause of tetany, and many theories have been advanced, some of the more important of these being the following:

1. The liver plays a rôle of primary importance.[37]

2. The symptoms are due to the absorption of products of bacterial decomposition from the intestine.[38]

3. The theory advanced by Wilson[39] and his co-workers is that a derangement of the acid-base equilibrium is the actual cause of the symptoms.

4. The theory that was first advanced by Vassale and Generali is that the products formed by the metabolism of the thyroid are neutralized by the action of the parathyroid gland. These authors believed that more severe tetany resulted from parathyroidectomy alone than from thyroparathyroidectomy, but other authors have not agreed with their view, nor with that of Rudinger[40] who held a somewhat similar view regarding thyroid-parathyroid balance.

5. A theory which has been widely held was first advanced in 1912 by Koch.[41] This is the so-called guanidine intoxication theory, which is based on the presence of methyl-guanidine and other bases in the urine following parathyroidectomy. Paton,[36] who has been the chief advocate of this theory, expressed the belief that tetany is due to a definite toxemia and that the secretion of the parathyroid glands controls the toxemia by the regulation of the production and destruction of guanidine and methyl-guanidine. Paton makes the following claims: 1. The symptoms produced by the administration of guanidine and methyl-guanidine are identical with those in cases of postoperative tetany. 2. Small doses of these substances markedly aggravate the symptoms of tetany. 3. The amount of these agents in the blood and in the urine is increased after parathyroidectomy.

Findlay and Sharpe[42] and Nattrass and Sharpe[43] observed an increase in the amount of guanidine in the urine in cases of tetany. The

35. Binger, C.: J. Pharm. & Exper. Therap. **10**:105 (Aug.) 1917.
36. Paton, N.: Edinburgh M. J. **31**:541 (Oct.) 1924.
37. Blumenstock, J., and Ickstadt, A.: J. Biol. Chem. **61**:91 (Aug.) 1924.
38. Dragstedt, L. R., and Peacock, S. C.: Am. J. Physiol. **64**:424 (May) 1923.
39. Wilson, D. W.; Sterns, T., and Thurlow, M.: J. Biol. Chem. **23**:89, 1915.
40. Rudinger, C.: Ergebn. d. inn. Med. u. Kinderh., 1908, p. 221.
41. Koch, W. F.: J. Biol. Chem. **12**:313, 1912.
42. Findlay, L., and Sharpe, J. S.: Quart. J. Med. **13**:433 (July) 1920.
43. Nattrass, F. J., and Sharpe, J. S.: Brit. M. J. **2**:238 (Aug. 13) 1921.

guanidine theory is strongly supported by Frank, Stern and Nothmann,[44] György and Vollmer,[45] Palladin and Grilliches [46] and others.

It is also claimed by Watanabe [47] and others that there is a direct relationship between the injection of guanidine and the level of calcium in the blood. Nelken,[48] Salvesen [49] and Collip and Clark [50] failed to confirm this opinion.

The one outstanding fact which has been established as evidence against the guanidine theory is that Collip and Clark observed guanidine intoxication in the presence of an overdosage of parathyroid hormone; that is, hypercalcemia fails to control tetany from guanidine poisoning while it is incompatible with tetany following parathyroidectomy.

A method for estimating the activity of the parathyroid glands based on guanidine destruction was advanced in 1923 by Vines,[51] and was found by White and Cameron [52] to have negligible activity when tested with Collip's active parathyroid extract.

6. The calcium theory of the function of the parathyroid gland was advanced in 1909 by MacCallum and Voegtlin,[53] and was confirmed in 1923 by Salvesen,[49] who expressed the belief that the parathyroid glands control the calcium content of the blood. In 1924, Greenwald [54] stated that there are only two well-authenticated metabolic changes after parathyroidectomy; one is the lowered calcium content of the blood serum, and the other, the diminished excretion of phosphorus in the urine.

In his recent work, Collip [55] has proved conclusively that the outstanding function of the parathyroid glands is their specific effect on the concentration of calcium in the blood. It appears now to be established that the activity of the parathyroid glands can be measured to a great extent by the level of the blood calcium.

That it may not, however, be possible to make serum calcium an absolute gage of the degree of activity which is indicated by clinical observations is suggested by the following reported cases.

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44. Frank, E.; Stern, R., and Nothmann, M.: Ztschr. f. d. ges. exper. Med. **24**:341, 1921.
45. György and Vollmer: Arch. f. exper. Path. u. Pharmakol. **105**:200, 1922.
46. Palladin, A., and Grilliches, L.: Biochem. Ztschr. **146**:458, 1924.
47. Watanabe, C. K.: J. Biol. Chem. **36**:531 (Dec.) 1918.
48. Nelken: Ztschr. f. d. ges. exper. Med. **32**:343, 1923.
49. Salvesen, H. A.: J. Biol. Chem. **56**:443 (June) 1923.
50. Collip, J. B., and Clark, E. P.: J. Biol. Chem. **67**:21 (March) 1926.
51. Vines, H. W. C.: Brit. M. J. **2**:559 (Sept.) 1923.
52. White, F. D., and Cameron, A. T.: Tr. Roy. Soc. Can. **19**:45, 1925.
53. MacCallum, W. G., and Voegtlin, C.: J. Exper. Med. **11**:118, 1909.
54. Greenwald, I.: J. Biol. Chem. **59**:329, 1924.
55. Collip, J. B.: Medicine **5**:1, 1926.

Within the last year, three cases of mild chronic tetany in which the blood calcium is within normal limits, have come to my notice. Surgical measures had not been employed on any of the three patients, all of whom were women between 30 and 40 years of age. None of them had goiter, nor were they pregnant. One showed nervous excitability, with twitching of the muscles of the forearm, occasionally accompanied by slight pain. These symptoms had been present almost daily for four months. The second and third patients complained of slight numbness and tingling of the fingers and small, painless, cramplike contractions of the muscles of the fingers; in one patient, the muscles of the forearm were occasionally affected. The symptoms had been present for eight and two weeks, respectively. The first patient was seen in March, 1927, and the other two in September, 1927. In none of the patients was there a positive Chvostek's nor Trousseau's sign present, and the serum calcium was normal in all three. These patients were all given parathyroid extract, 0.2 grains (0.01296 Gm.) three times daily for a period of two weeks, with the results that the symptoms entirely disappeared. The first patient had slight symptoms for ten days; the symptoms of the other two completely disappeared in four and seven days, respectively.

In the patient who was seen in March, recurrence of the symptoms was not noted when she was again observed three months later. The second patient was free from symptoms one month after the treatment had been discontinued, and the third patient has not been heard from since two weeks after the completion of the course of treatment with thyroid extract. Although there may have been some doubt as to the diagnosis, the symptoms were suggestive and disappeared on treatment.

Another condition opposite to the foregoing one may occur. Patients with definite chronic postoperative tetany may be free from symptoms while the serum calcium remains about 8 mg. per hundred cubic centimeters, or slightly above this level, whereas if it falls below 8 mg., the definite classical symptoms occur. All who are familiar with chronic postoperative tetany have undoubtedly frequently observed this sequence of events.

A third group of cases shows that symptoms of tetany may remain for several days after the serum calcium has returned to the normal level. This condition may, however, be due to the fact that although the serum is normal, the amount in the tissues is still slightly deficient. A case seen recently will illustrate this point.

A married woman, aged 37, had had a thyroidectomy for hyperthyroidism. On the morning of the fourth day after operation, she complained of numbness of the fingers and toes and stiffness of the fingers. She showed a mild degree of carpal spasm and a moderately marked Trousseau's sign. The calcium was 7.9 mg. per hundred cubic centimeters. Two cubic centimeters of parathyroid extract-Collip (Lilly) was given subcutaneously and the symptoms promptly subsided. Because of the presence of mild symptoms, 1 cc. of parathyroid extract-Collip was given on the fifth, sixth, and seventh days after operation. The level of the calcium rose to 10.4 mg. and further medication was not given. On the eighth day after operation, when the serum calcium was 10.3 mg., the patient described a sensation of stiffness and slight numbness in the fingers. The following day, she said that her

fingers felt "as though they had just been asleep," the serum calcium being 10.8 mg. On the tenth day, she described a slight tingling of the fingers as though "they had been cold and were just getting warm again." The serum calcium on this day was 10.5 mg. The symptoms had entirely disappeared on the eleventh day after operation and they did not recur during observation through the following week.

These observations suggest that the smaller changes in the function of the parathyroid glands cannot always be detected by changes in serum calcium; however, I believe that it is the best method available.

THE BLOOD CALCIUM IN HYPOTHYROIDISM AND HYPERTHYROIDISM

In the literature may be found many references to the level of serum calcium in cases of hypothyroidism and hyperthyroidism. Hall [56] stated that the content of this salt in the blood is diminished in both conditions.

Herzfeld and Neuberger [57] reported determinations of the serum calcium in nineteen cases of hyperthyroidism. In one third of these cases, the level was normal, and in two thirds, it was either above or below normal.

In a study of blood calcium levels in twenty-six cases in which thyroidectomy was performed, Rabinowitch [58] noted a constant drop following operation. Neither symptoms of tetany nor any parathyroid tissue was found in the operative specimen of any of the cases. He assumed the cause of the diminished serum calcium to be trauma of the parathyroid glands caused by manipulation.

In the experiments reported in this paper, the serum calcium has been measured in cases of hypothyroidism and hyperthyroidism. Cases in which there were symptoms of tetany have not been included.

The method used was a modification of the Kramer-Tisdall method, the permanganate solution being 0.01 normal. By this method, it may be noted that when one uses 2 cc. of serum an error of 0.4 mg. per hundred cubic centimeters will be made by an error of one drop of fluid in titrations. I have tried to have the titrations correct to one half of a drop in all experiments. Duplicate determinations were done in twelve cases, and the greatest difference found between two determinations on the same serum was 0.4 mg. This difference was found in two of the twelve cases. In one, there was a difference of 0.3 mg.; in four, a difference of 0.2 mg. The results were identical in five.

The normal level of serum calcium was considered by Kramer and Tisdall [59] to be from 9.5 to 10.5 mg. per hundred cubic centimeters.

56. Hall, S. H.: Med. Press **119**:436, 1925.
57. Herzfeld, E., and Neuberger, J.: Deutsche med. Wchnschr. **1**:1324, 1875.
58. Rabinowitch, I. M.: J. Lab. & Clin. Med. **9**:543 (May) 1924.
59. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475, 1926.

Kramer and Howland [60] reported a normal variation of from 9.3 to 9.9 mg. Watchorn [61] considered the range from 10 to 10.8 mg. to be normal, and Schamberg and Brown [62] cited normal cases with a variation of from 9.7 to 11.3 mg. I have considered the extreme normal range of serum calcium to be from 9 to 11 mg. per hundred cubic centimeters.

EXPERIMENTAL WORK

In the first experiment, ninety-six determinations of the serum calcium were made in twenty-seven cases of hyperthyroidism in which bilateral ligation of the superior thyroid artery was performed. The results in this group of determinations are shown in chart 1. The ligations in each case were three days apart and determinations of the serum calcium were not made on the intervening days.

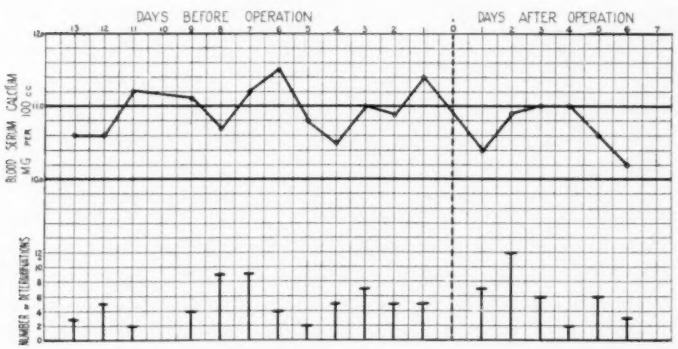

Chart 1.—The relationship between ligation of the superior thyroid arteries and the blood serum calcium—ninety-six determinations in twenty-seven cases. The ordinates represent the serum calcium in milligrams per hundred cubic centimeters; the deep black lines, the number of patients on whom determinations were made on a given day; the abscissae, days before and after operation. Minus one (—1) means one day before the first ligation, and plus one (+1), one day after the second ligation.

It will be noted that definite changes in the serum calcium level did not result from this operation. Of the sixty determinations which were made before operation, the average value was 10.9 mg., while the average value in thirty-six determinations following these operations was 10.8 mg. per hundred cubic centimeters.

60. Kramer, B., and Howland, T.: J. Biol. Chem. **43**:35 (Aug.) 1920.

61. Watchorn, E.: Quart. J. Med. **18**:288 (April) 1925.

62. Schamberg, J. F., and Brown, H.: Inorganic Salts in Blood as a Measure of Liver Damage in Treatment with Arsphenamines, Arch. Dermat. & Syph. **9**:368 (March) 1924.

In the second experiment, thirty-five determinations of the serum calcium were made in eighteen cases of hyperthyroidism in which lobectomy was performed. In 59 per cent of the cases, a fall in serum calcium followed this operation, the lowest levels occurring from the fourth to the sixth day after operation. Of twenty determinations made before operation, the average level was 10.8 mg., while of fifteen postoperative determinations, the average value was 10.5 mg., an average fall of 0.3 mg.

In the third experiment, 177 serum calcium values were established in 54 cases of thyroidectomy. A fall in serum followed this operation in 76 per cent of the cases. The average results in these cases are shown in chart 2. The average calcium level in ninety-one determinations

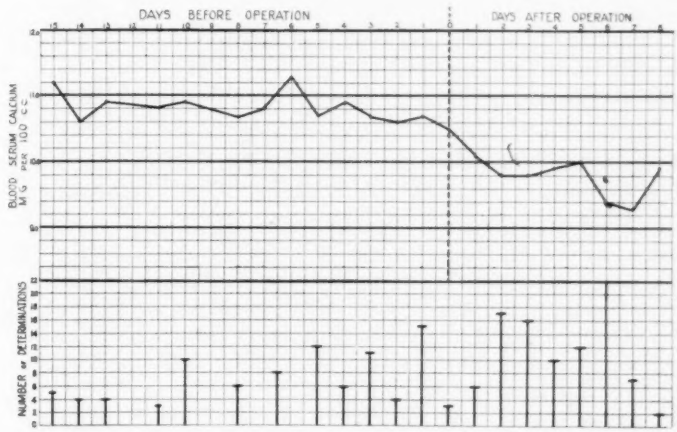

Chart 2.—The effect of thyroidectomy on blood serum calcium in 177 determinations in 54 cases. The numbers represent the averages of the serum calcium levels in several cases on the same day relative to the operation. The black upright lines represent the number of cases on which determinations were made on a given day.

made before operation was 10.7, while the average of eighty-six determinations made after operation was 9.7, an average fall of 1 mg.

In 75 per cent of the cases, the fall was definite from the first to the eighth day after operation.

The fourth experiment includes 139 serum calcium levels in as many cases in which the basal metabolic rate was determined coincidentally, the blood for the test being taken in every case in the morning before the ingestion of food and within one hour after the metabolism test. Chart 3 has been complied in the same manner as the two preceding charts, the abscissae here representing the basal metabolic rate.

All calcium levels in cases in which the metabolic rates were within 5 per cent of one another have been averaged and plotted as one point. The metabolic rates varied from — 30 to + 75 per cent. The chart shows that there has been neither a definite rise nor fall in serum calcium in either hypothyroidism or hyperthyroidism. The average serum calcium in thirty-two cases, in all of which the basal metabolic rate was below zero, was 10.9 mg. per hundred cubic centimeters. The average serum calcium in 105 cases, in which the basal metabolic rate varied from 0 to + 75, was 11 mg. per hundred cubic centimeters.

In 5.1 per cent of all cases, there was a hypercalcemia. This condition occurred evenly in hyperthyroidism and hypothyroidism in all cases in which a basal metabolic rate was determined.

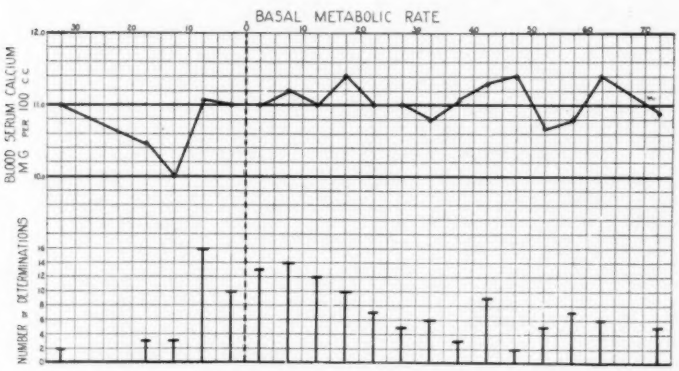

Chart 3.—The relationship between the blood serum calcium and the basal metabolic rate in 139 cases. The abscissae represent the basal metabolic rate.

I consider that the fall in serum calcium which follows thyroid lobectomy and thyroidectomy is due to three main factors: (1) trauma which the parathyroid glands suffer from manipulation during operation; (2) disturbance in the blood supply of the parathyroid glands, from edema about the operative field, from direct trauma or infection; (3) the removal of parathyroid glands which have been on the anterior surface of the thyroid gland. In 1 per cent of all cases, hypocalcemia occurred; in each case it was present in a patient who was convalescing from thyroidectomy and with one exception it was found on the sixth or seventh day after operation.

SUMMARY

I have reviewed some of the more important articles dealing with the parathyroid glands and their relation to the thyroid. The points which seem of importance in regard to thyroid-parathyroid interrela-

tionship are: 1. Hypertrophy of the thyroid or of the parathyroid glands may be provoked in either by the suppression of the other. 2. Thyroid extract has been observed to have a beneficial effect in the treatment of the subjects with tetany. 3. Definite changes in the parathyroid glands have not been found in hyperthyroidism.

The function of the parathyroid glands has been measured by determinations of the serum calcium level. In cases in which a ligation of the superior thyroid arteries was made, a definite drop in serum calcium did not occur. A fall of this level was noted after lobectomy, and a much more marked fall occurred after thyroidectomy. The serum calcium was found to be normal in 94 per cent of 139 cases of hypothyroidism and hyperthyroidism, and no relationship to the basal metabolic rate has been observed.

In the experiments reported, I have found nothing to indicate an abnormal functioning of the parathyroid glands in either hypothyroidism or hyperthyroidism except in cases in which there has been actual trauma or removal of these glands. I have not found any indication for the use of parathyroid hormone in cases of hyperthyroidism.

PANCREATIC FUNCTION

II. THE PANCREATIC ACTIVITY IN DIABETES MELLITUS *

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In 1788, Cawley [1] reported an intimate relationship between the sugar-regulating function and the pancreas and considered pancreatic disease an important factor in the etiology of diabetes. This was confirmed by various workers, such as Bright, Bouchardat, Friedreich, Bamberger, Frerichs, Senator, Seegen and others. The reports, however, were not more than statistical statements until Lancéraux (1877), on the basis of many clinical and anatomic observations, described a special form of diabetes called diabète pancréatique or diabète maigre. This form is characterized by a sudden onset, a malignant course and a special tendency to the complication of tuberculosis. The epoch-making discovery of von Mering and Minkowski [2] in 1889, as well as the independent observations of N. de Dominicis,[3] that complete extirpation of the pancreas in dogs always caused pronounced glycosuria, had made a marked effect on the development of the investigation of diabetes. Following the suggestion of Lancéreaux, Bouchard and Gilbert in France, diabetes has been classified anatomically into pancreatic, hepatic and nervous forms. As to the histologic alterations in the pancreas, opinions diverged at first. Some authors, such as Lépine and Lemoine, thought that the lesion of the acinous cells was the predominating feature, while many others, especially after the work of E. L. Opie, directed their attention to the insular involvement. The typical pathologic process of the disease was first noted by Opie [4] in 1901, and later by Weichselbaum

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1. Cawley, cited by Labbé and Réchard: Les troubles de la sécrétion externe du pancréas dans le diabète sucré, Arch. d. mal. d. l'app. digestif **16**:867, 1926.

2. Von Mering, J., and Minkowski, O.: Diabetes nach Pankreasexstirpation, Zentralbl. f. klin. Med., 1889, p. 393; Arch. f. exper. Path. u. Pharmakol. **26**:371, 1889.

3. De Dominicis: Studiisperim. intorno agli effeti delle estirpazione del pancreas, Gior. int. delle sc. med., 1889, p. 801.

4. Opie, E. T.: Diabetes Mellitus Associated with Hyaline Degeneration of the Islands of Langerhans of the Pancreas, Bull. Johns Hopkins Hosp. **12**:263, 1901.

and Stangl,[5] who described the hydropic degeneration and vacuolization of the cells of the islands of Langerhans.

The obtaining of the pancreatic hormone from the wasted glands of animals by ligating the pancreatic duct according to the method of Banting,[6] and the preparation of insulin from the islands of Langerhans of certain fish, in which they are separated from the zymogenous tissue, according to the method of Macleod,[7] have removed all doubt as to the correctness of the theory concerning the islands of Langerhans. Thus, a deficiency of the internal secretion of the pancreas as the immediate cause of the glycosuria is incontestably proved, but the extent to which other organic functions are involved still remains a question. According to Allen,[8] in most, if not in all, cases of diabetes mellitus, there must have been a preceding disease of the pancreas. This investigator expressed the opinion that such pancreatic disease usually involves damage to both the insular and the acinous cells. According to Joslin,[9] although proof of the cause of the disease is still lacking, an antecedent pancreatitis would appear to be the most logical explanation.

In view of the foregoing data, it is evident that in diabetes mellitus, in addition to the known diminution of the internal secretion of the cells of the islands of Langerhans, there may also be abnormalities in the external secretory activity of the pancreas.

Okada [10] reported, perhaps for the first time, that in severe cases of diabetes a small amount of trypsin is often found in the duodenal contents. Von Noorden [11] reported that in some cases of diabetes there was a diminution in the trypsin and lipolytic enzymes present in the duodenal fluid, notwithstanding the fact that the feces still remained normal. Katsch and Friedrich [12] found a significant decrease of trypsin and lipase in only one of five cases. Langanke [13] examined four patients with severe diabetes and found that all of them showed remarkably low activity of trypsin and lipase while the amylolytic activity remained normal.

5. Weichselbaum, A., and Stangl, E.: Zur Kenntnis der feineren Veränderungen des Pankreas bei Diabetes Mellitus, Wien. klin. Wchnschr. **14**:968, 1901.

6. Banting, F. G., and Best, C. H.: The Internal Secretion of the Pancreas, J. Lab. & Clin. Med. **7**:251 (Feb.) 1922.

7. Macleod, J. J. R.: The Source of Insulin, J. Metab. Research **2**:149, 1922.

8. Allen, F. M.: The Pathology of Diabetes, J. Metab. Research **1**:165, 1922.

9. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 3, Philadelphia, Lea & Febiger, 1923, p. 137.

10. Okada, S.: Ueber die Pankreassekretion bei Sekretionsstörungen des Magens, Mitt. d. med. Fak. d. Kaiserl. Univ. z. Tokyo **13**:157, 1914.

11. Von Noorden: Die Zuckerkrankheit, ed. 7, 1915.

12. Katsch, G., and Friedrich, L. v.: Bauchspeichelfluss auf Aetherreiz, Klin. Wchnschr. **1**:112, 1922.

13. Langanke, E.: Untersuchungen über die Fermente des Pankreas vor und nach Injektion von Aether ins Duodenum, Klin. Wchnschr. **1**:1458, 1922.

Jones, Castle, Mulholland and Bailey [14] made a comprehensive report on the pancreatic and hepatic activity in diabetes mellitus. They examined an unselected group of sixty-eight diabetic patients for evidence of alteration in pancreatic or hepatic activity. They found a diminution in the activity of one or more of the pancreatic enzymes in nearly one half of their cases. The striking fact in these observations is that amylolytic activity was apparently diminished in only 9 per cent of the cases, whereas proteolytic activity and lipolytic activity showed definite reductions below the minimum normal level in over a third of the cases. The elimination of bile pigment in the duodenal contents was abnormally high in about three fourths of the cases. In nearly one third of the cases there were associated abnormalities of the enzymes and pigment. The enzymatic abnormalities are probably due to associated anatomic and functional changes in the acinar tissue of the pancreas. Undernutrition may play a part in the production of such changes, but it is not the sole cause. It is suggested that the diminution of enzymatic activity may result in disturbances due to improper digestion of fat and protein. Efficient insulin therapy, with its associated increase in food intake and improvement of tissue function, seems to be associated with a reduction in pancreatic and hepatic abnormalities. Acidosis produces a marked disturbance in the enzymatic activity in the pancreas and also in the function of the liver. The improvement in pancreatic and hepatic function, as measured by changes in the enzymatic activity and elimination of bile pigment, following recovery from acidosis, is striking, and illustrates the degree to which acidosis affects all bodily functions. Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19 per cent of the cases in this series. In adults, cholelithiasis is probably one of the most important etiologic factors in diabetes mellitus. Bargy,[15] Labbé and Réchad [16] also made examinations to determine the enzymatic activity of the duodenal content in cases of diabetes mellitus. Labbé and Réchad could not find normal enzymatic activity in any of their ten cases. They examined the proteolytic and lipolytic activity and found that both enzymes were insufficient in six cases; in three cases only the proteolytic was diminished, and in one case, only the lipolytic activity. The insufficiency of the external secretion of the pancreas is often not apparent clinically, but is revealed only in the laboratory examination, while in

14. Jones, C. M.; Castle, W. B.; Mulholland, H. B., and Bailey, F.: Pancreatic and Hepatic Activity in Diabetes Mellitus, Arch. Int. Med. **35**:315 (March) 1925.

15. Bargy, R.: Insuffisance pancreatique externe chez les diabetiques, étudiée par l'evaluation de l'activité fermentaire dans le liquide duodénal, Thèse de Paris, 1926.

16. Labbé, M., and Réchad: Les troubles de la sécretion externe du pancreas dans le diabète sucré, Arch. d. mal. d. l'app. digestif **16**:865, 1926.

some cases it is shown by the symptoms of indigestion and severely impaired regulation of metabolism of sugar. This is why the diagnosis of pancreatic diabetes should be made with caution. Hernando [17] also found a diminution of the enzymatic activity of the duodenal fluid in a great many cases of diabetes. On the other hand, Isaac-Krieger [18] did not find a diminution of the duodenal contents in seven cases. Deusch and Drost [19] examined the enzymatic activity of the duodenal contents in ten cases of diabetes of various degrees of severity in persons of different ages and did not find any deviation from that in control persons. They expressed the opinion that disturbance of the external secretion of the pancreas in cases of diabetes is exceptional and only found in cases in which primary enterogenic involvement of the pancreas (pancreatitis, cysts or stone formation) or a universal pancreatic involvement (arteriosclerosis, syphilis) exists. From their results, they attempted to classify the diabetes as a primary, chiefly kryptogenetic diabetes affecting the islands of Langerhans and a secondary, symptomatic diabetes with pancreatic involvement. Kusnetzow and Michailowa [20] examined six cases of diabetes and found in four cases the tryptic and lipolytic activity distinctly diminished while amylolytic activity showed normal values. The two other cases were normal in all enzymatic activity.

The opinions of the aforementioned authors vary widely. Some consider that the enzymatic activity of the duodenal contents is always abnormal in diabetes; others, that it is never abnormal and still others noted, individually and collectively, every modification of point of view between the two extremes. This state of affairs shows that it is important to make more exact and careful examinations in order to solve this problem. It seems necessary to consider why this controversy arose. Certain factors in the cases examined, i.e., severity and duration of the disease, age, nutrition, etc., might have an influence on the results. The most important factor, however, seems to be the method employed. As we mentioned in our first paper, all quantitative tests applied hitherto meet theoretical as well as real objections. Therefore, we wish to publish the results we obtained by using our newly devised method,[21] which might be considered for the first time as a quantitative test of the pancreatic secretion in its real meaning. This method was published in the first paper of this series.[21]

17. Hernando, cited by Deusch and Drost: Klin. Wchnschr. **6**:2180, 1927.

18. Isaac-Krieger, cited by Deusch and Drost: Klin. Wchnschr. **6**:2180, 1927.

19. Deusch, G., and Drost, E.: Innere und äussere Sekretion des Pankreas, Klin. Wchnschr. **6**:2180, 1927.

20. Kusnetzow, N. W., and Michailowa, S. J.: Die Sekretionstätigkeit der Bauchspeicheldrüse im Verlaufe von Erkrankungen der Gigestionsorgane, Arch. f. Verdauungskr. **40**:41, 1927.

21. Okada, S.; Sakurai, E.; Imazu, T., and Kuramochi, K.: Pancreatic Function: I. The Quantitative Estimation of the Pancreatic Secretion. Arch. Int. Med. **42**:270 (Aug.) 1928.

CLINICAL MATERIAL

The cases under consideration consisted of an unselected group of twenty-one patients with diabetes mellitus taken from the wards of the University Hospital of Tokyo. The youngest patient was 28 years of age, the oldest, 72. The average age was 45 years. Of the twenty-one patients, two-thirds were over 40 years of age and five over 50. There was a pronounced preponderance of the cases in men, sixteen being in men and five in women. The average known duration of the disease was about two years. In a few patients, the disease had apparently existed for only one or two months, and in one case it must have been present over ten years. Four patients were examined while definitely acidotic; four patients had a known history or had been suffering from cholecystitis or jaundice. Exophthalmic goiter was present in two patients, one of whom was suffering severely when examined. Two patients were suffering extremely from nephritis and two from pulmonary tuberculosis.

OBSERVATIONS

Examination of the table reveals that some patients showed normal enzymatic activity of the duodenal return while others showed only a trace of the activity, so that it seemed illogical to compute an average. Of the twenty-one cases in which thirty-three estimations were made, fourteen cases (67 per cent) showed proteolytic efficiency (a three hours' collection); seven cases (33 per cent) amylolytic efficiency, and twelve cases (57 per cent) lipolytic efficiency values below our minimal normal limits. In six cases (29 per cent), the efficiency of the three enzymes was within normal limits; in five cases (24 per cent), all enzymes were abnormally low. From the enzymatic activity, we found the proteolytic activity in nine cases (43 per cent), the amylolytic activity in four cases (20 per cent) and the lipolytic activity in nine cases (43 per cent) to be below our minimal normal limits. In ten cases (48 per cent), the activity of the three enzymes was within normal limits, and in three cases (14 per cent), abnormally low. The percentage of abnormalities for the total efficiency is somewhat higher than that for the enzymatic activity, owing to the fact that the amount of the duodenal return was distinctly low in several cases. Some cases showed abnormally low enzymatic activity with a normal amount of duodenal return; some showed normal enzymatic activity with a scanty amount, and others showed abnormally low enzymatic activity as well as an abnormally low duodenal return. The average amount of the duodenal return (when estimated several times for the same case, the average of the case was used for the calculation of the general average) was 87 cc. (71 per cent of the normal average). The average amount of the bile pigment in three hours was 12.2 mg., which is slightly lower than

the normal average (14.9 mg.), while the concentration of that is a little higher (14 mg. per cent, while the normal average was 12.1 mg. per cent). We could not detect any abnormalities in the pigment, though a slight difference from the normal in average was perceived. The abnormality of the enzymatic activity does not seem to exhibit any direct proportion to the severity of the impairment of the metabolism of sugar, duration of the disease, kind of diet, calories taken on previous days and acidosis. The nature of the involvement seems to be the most essential factor. The noticeable fact is that patients over 59 years of age (five cases) showed all abnormalities of the enzymatic efficiency for one or more of the enzymes. Perhaps these abnormalities in persons past middle life are due to some serious damage to both the insular and the acinous cells as the result of pancreatic fibrosis and cellular degeneration or sclerosis. The most instructive cases are cases 6 and 10 and probably the case of pancreatic cancer without glycosuria. Somewhat detailed reports of these three cases are given as representative of cases of pancreatic involvement.

REPORT OF CASES

CASE 6.—Y. S., a farmer, aged 43, was admitted to the hospital on Oct. 29, 1926, complaining of jaundice, glycosuria and emaciation. There was nothing of special importance in the family history. So far as was known, he had not had measles; the patient had been vaccinated several times. He had had typhoid fever at the age of 7, which cleared up in a month. He had married at the age of 20. A syphilitic condition of the left eye occurred when he was 26; it had healed in three weeks, leaving some weakness of vision and central scotoma. He said that he had not had venereal disease, but the Wassermann reaction was strongly positive. He drank wine only occasionally, and used tobacco moderately.

Since November, 1925, he had complained of fatigue and loss of appetite; later, he was emaciated. Since January, 1926, he had also complained of thirst and hunger, and polyphagia, polydipsia and polyuria were manifested. He thought that he must have diabetes mellitus, judging from the description of the condition in the newspapers. He visited a hospital, and found that his diagnosis was correct. Since April 20, antidiabetic treatment had been given, but after that he complained of lack of appetite, nausea, and pyrosis. On May 20, he was admitted to the hospital; he was placed on a restricted diet, and insulin was administered. Following this treatment, the urine became free from sugar. Diarrhea did not occur. Since October 1, he had noticed that the urine was brown. On October 3, a physician diagnosed the condition as jaundice which continued to grow worse until October 15 to 16, after which it gradually became better. On October 29, he had visited the dispensary of the hospital, and had been admitted to the hospital.

He was well built, but showed signs of slight emaciation. The skin was somewhat pale, with a moderate degree of jaundice, and the amount of subcutaneous fatty tissue was reduced. According to the method of Meulengracht, the degree of the jaundice was 68 times positive. The pupillary reflexes were normal. Some of the teeth were missing or were carious. The tonsils were in good condition. The pulse rate was 60, and there was no fever. Abnormalities of the head, neck and extremities were not detected. The apexes were somewhat dull, otherwise the lungs were intact. The size of the heart was normal; the first sound at the apex was impure and the second pulmonic sound was accentuated. The abdomen

was increased in its transverse diameter and was distended in the epigastric region. The right lobe of the liver was palpable one and a half fingerbreadths under the arch of the right rib in the right nipple line. The border was rather hard. The surface was slippery and did not show any tenderness. The left lobe was palpable two fingerbreadths under the ensiform. The consistency of both lobes was not so hard as in cancer. The gallbladder was palpable two fingerbreadths under the arch of the right rib and was somewhat smaller than a fist. It was soft and elastic. The spleen was just palpable. The pancreas was palpable in the midline between the ensiform and the umbilicus, about 3 cm. in breadth; some tenderness was felt and the consistency was somewhat increased. Ascites was not noted. The stomach when swollen by effervescent powder extended from the middle of the ensiform and umbilicus to the umbilical line, the right border extending three fingerbreadths right of the middle line. Roentgen-ray examination did not show any abnormality of the stomach. The free hydrochloric acid of the contents of the stomach one hour after an Ewald-Boas test meal was 34 and the total acidity 64. The sugar tolerance was not exceeded until more than 60 Gm. of boiled rice had been ingested. When 100 Gm. of boiled rice was ingested the blood sugar rose to 0.306 per cent and the urinary sugar to 1.2 per cent. The threshold of sugar tolerance was 0.2 per cent. The duodenal contents were examined ten times and were almost always greenish; culture showed *Staphylococcus albus*. The enzymatic activity of the duodenal contents was extremely reduced. When our three hours' test method was used, the tryptic efficiency showed from 0.28 to 1.2 kilo-units, the amylolytic efficiency from 1.1 to 13.6 kilo-units and the lipolytic efficiency from 1.7 to 6.2 kilo-units. The degree of the enzymatic activity was 0 to 20, 0 to 146 and 3 to 596 units, respectively. Hypodermic injection of 10 units of insulin (Toronto) caused marked hypoglycemia, but there was scarcely any increase in the external secretion. The feces were voluminous; when the patient was admitted they were porcelain-colored, but later they became somewhat greenish. Microscopically, a moderate amount of striated muscle fibers and steatorrhea were perceived during the whole course of the disease. The Kashiwado test gave a positive result; the Wassermann reaction was strongly positive. When the patient was admitted, a slight anemia existed, which later improved decidedly. The amylolytic activity of the blood serum, according to the method of Wohlgemuth, was 8 degrees and that of urine was 32 degrees, i. e., there was no increase of the amylolytic activity of the blood serum and urine. The jaundice lessened and disappeared in a month. The liver gradually became smaller; after from fifteen to sixteen days, the left lobe was no longer palpable, while after twenty days the gallbladder also was not palpable, only the right lobe being barely felt under the arch of the right rib. The pancreas was barely palpable after two months. Intensive treatment with Meltzer-Lyon's duodenal drainage and applications of mercurial ointment and iodide was tried; when the patient was discharged on Jan. 27, 1927, the Wassermann reaction was still positive and the enzymatic activity was even less than when an examination was made on July 29, 1927, nine months after admission. The insulin treatment (35 units per day for eleven days) did not cause the diabetes to improve nor the enzymatic activity of the duodenal return to increase. Loewi's pupillar test was often tried, with negative results.

From the symptoms in this case, it is evident that it belongs to the type of so-called pancreatic diabetes. In view of the fact that the duodenal return was always greenish and contained *Staphylococcus albus*, it seems likely, at first glance, that the pancreatic involvement was caused

by contamination from the bile and pancreatic ducts. But diabetes existed long before the biliary tract disease and did not improve when the latter condition disappeared. It seems probable that syphilis had some special relation to pancreatic involvement, though it was not definitely proved.

CASE 10.—S. K., a functionary, aged 49, was admitted to the hospital on April 10, 1927, complaining of thirst, cough during the night, fatigue and lack of appetite. The family history showed that the elder sister died of cholecystitis and peritonitis and the elder brother of beriberi. The patient had had smallpox when 7 years of age, measles when 11, ascariasis from 10 to 13, malaria when 13, gonorrheic gonitis when 21 and typhoid fever when 31 or 32. He said that he had not had syphilis, but two years before admission he had suffered from an eye disease, and the Wassermann reaction was strongly positive. He was given ten injections of arsphenamine, and the condition improved. He took wine moderately and tobacco excessively; he also liked sweets. He had broken the left clavicle when he was 43 years old.

In March, 1919, he had complained of thirst; a physician had examined the urine and had diagnosed the condition as diabetes mellitus. For about three years he had been fed on a restricted diet. When rice had been eliminated from his diet, he had become emaciated and weary, but he had recovered when rice was again added to the diet. In 1921, he had been advised to take care of himself as his lungs were diseased. Since February 12 or 13, 1927, he had suffered from pulmonary tuberculosis and had been confined to bed. He coughed and expectorated sputum sometimes tinged with blood almost constantly. He was feverish from the beginning and at times his temperature was as high as 39 C. (102.2 F.). Sweating at night was especially noticeable when he took a drug. He complained of almost continuous headache, light sleep and constipation.

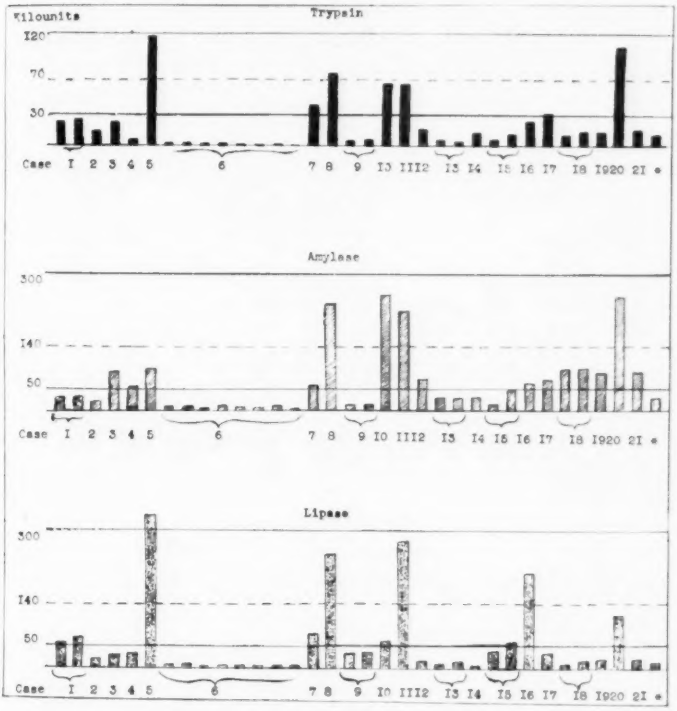
Examination showed a man of rather small stature, somewhat weakly built and with an extremely reduced amount of subcutaneous fatty tissue. The muscles were considerably relaxed. The skin was hot and normally humid. The facies was somewhat dull; the complexion was normal. The pulse rate was 90, and the beat was faint and regular. The arterial wall was rather hard. Respiration was costal abdominal. The tendon and skin reflexes were normal. The tongue was wet, but not furred and the pharynx was somewhat injected. The chest was symmetrical and the supraclavicular and infraclavicular regions were depressed. The heart was normal except for a slight accentuation of the second pulmonic sound. The dulness of the right lung extended from the apex to the first rib and in the left lung, to the second rib. In the back, the dulness extended from the apex of the right lung to the second rib and to the fourth rib on the left side. Respiratory sounds were weak and on the left side, anteriorly and posteriorly, many small and medium sized râles were audible. The extremities did not show any abnormalities except marked weakness. The sputum was slimy and mixed with blood. Elastic fibers were detected and according to Gaffky's scale, no. 5 or 6 tubercle bacilli were found. The urine was yellowish brown, somewhat turbid and acid; there was a trace of protein, 4 per cent of sugar and no acetone bodies. The blood count showed 4,740,000 red blood cells, 82 per cent hemoglobin and 7,100 leukocytes, of which 70.5 per cent were polymorphonuclear neutrophils; 24 per cent, lymphocytes, and 5.5 per cent, mononuclears and transitory cells. The Wassermann reaction was weakly positive. The blood sugar rose to 0.315 per hundred cubic centimeters when 50 Gm. of bread and 200 cc. of milk were ingested. The fever continued almost two months with fluctuations; on April 13, 1927, when

the duodenal return was examined, it showed 37.6 C (99.7 F.) in the morning and 39.2 C. (102.6 F.) in the afternoon. The tryptic efficiency of a three hours' collection was 67.7 kilo-units, the amylolytic 253 kilo-units and the lipolytic, 58.3 kilo-units, i. e., normal values. Intensive treatment with insulin was tried, but, owing to the progress of the pulmonary tuberculosis, the patient died on May 7. At autopsy, the pancreas did not show much alteration; it weighed 85 Gm., and the consistency was somewhat increased; there was no atrophy. Microscopically, the connective tissue was increased to some extent, but it did not show any typical fibrosis. On the other hand, the islands of Langerhans had almost completely disappeared except at the tail of the pancreas where a few remnants were detectable. The observations that the acinar tissue was almost intact and the insular tissue was extremely atrophied coincide with the clinical observations of a normal external secretion and a highly disturbed regulation of metabolism of sugar.

Pancreatic Cancer.—T. O., a functionary, aged 45, was admitted to the hospital, Nov. 10, 1926, complaining of constipation and pain in the left hypochondrial region. The family history showed that the maternal grandmother died of apoplexy, the mother of pulmonary tuberculosis and the brothers of tuberculosis or heart disease. The patient had had measles when he was a small child, and had been vaccinated many times. He had had beriberi when 14, pyrosis when 20 and gonorrhea when 21. He said that he had never had syphilis. He smoked tobacco and liked sweets, but did not take much wine. Since he was over 10 years of age, he had suffered from constipation, a bowel movement occurring only every three or four days. On Aug. 25, 1927, as he had not had a bowel movement for four or five days he took castor oil, without effect; on the next day, he tried some powdered remedy, which caused nausea, vomiting and a movement. The following day he complained of pain in the hypochondriac region, which was not influenced by eating a meal. After several days, a similar pain occurred, and continued; there were fluctuations in intensity, but it was not colicky; and a bowel movement did not relieve the pain. In September, he was treated by a physician, and bowel movements occurred oftener. On October 6, after indigestion, he complained of severe pain in the left hypochondriac region, without vomiting. Since medicinal treatment did not relieve him, he was admitted to the hospital.

The patient was well nourished, vigorous and of medium height. The amount of subcutaneous fatty tissue was reduced. The pulse rate was 69, regular and moderately resistant to pressure. The systolic blood pressure was 129 mm. of mercury and the diastolic 74. The respiration was costal abdominal and regular. The skin did not show any abnormalities. The lymph glands were not palpable. The facial expression was natural. Sensibility and motility were normal, as were the pupillary reflexes. The lips showed nothing of particular importance; the tongue was slightly furred and wet. The pharynx and tonsils did not show any change. The lungs and heart were normal. The abdomen showed normal swelling. There was no venous congestion, pigment anomalies or edema. The region directly on the left side of the umbilicus and the left hypochondriac region were tender. The border of the stomach was one fingerbreadth under the ensiform and two fingerbreadths above the umbilicus and right parasternal line. The liver was not palpable. The pancreas was palpable four fingerbreadths over the umbilicus and was somewhat tender. The right kidney was barely palpable. The cecum, appendix, ascending, transversal, descending and sigmoid colons were palpable. The left side showed more or less tenderness. The extremities were normal in general. The tendon reflexes were exaggerated. The urine was yellowish, clear and alkaline with a specific gravity of 1.007 and it did not contain protein, sugar,

acetone bodies, bilirubin or urobilin. There was a trace of urobilinogen and indican. The sediment did not show any abnormalities. Parasites' eggs were not detected in feces. The Weber blood test of the feces was negative, but the Adler and Boas tests were weakly positive. The stomach contents were collected fractionally after a test breakfast and were found to be normal (free hydrochloric acid 45 and total acidity 66 one hour after the test breakfast). The duodenal contents were examined on Nov. 19, 1926, and the total tryptic efficiency was 10.9 kilo-units; amylolytic, 26.4 kilo-units, and lipolytic, 10.5 kilo-units; i. e., the efficiency of the three enzymes was diminished. The highest activity of trypsin



Enzymatic efficiency of the duodenal return in diabetes mellitus. The star indicates cancer of the pancreas.

was 320 units, of amylase 931 and of lipase 400; i. e., there was a decrease in the tryptic and lipolytic activity. The blood count showed 4,576,000 red blood cells, 68 per cent hemoglobin and 7,600 leukocytes, of which 61.6 per cent were polymorphonuclear neutrophils, 32.4 per cent, lymphocytes and 6 per cent mononuclears. Roentgen-ray examination of the intestine showed an enormous accumulation of gas in the left flexure and descending colon. The pain in the left hypochondriac region was attributed to this distention by gas, so that the patient was treated intensively for constipation, but without effect. Moreover, we could feel a tumor

Case, Name, Sex,* Age	Date	Stimulant† Introduced Into the Duodenum¶	Amount of Duodenal Return in 3 Hours, Cc.	Degree of Enzymatic Activity‡: Trypsin 1 Hour Unit	Trypsin 2 Hour Unit	Trypsin 3 Hour Unit	Amylase 1 Hour Unit	Amylase 2 Hour Unit	Amylase 3 Hour Unit	Lipase 1 Hour Unit	Lipase 2 Hour Unit	Lipase 3 Hour Unit	Trypsin in 3 Hours, Kilo-Unit	Amylase in 3 Hours, Kilo-Unit	Lipase in 3 Hours, Kilo-Unit
1. I. N. ♂, 42	10/27/26	Alcohol	42.8	800 500	500	500	347	1047	1393	1953 1029	1017	775	23.2	27.6	53.6
	11/ 3/26	Alcohol	57.7	500 200	500 500	100 50	510	438	306	1250 426	624 1150	300 100	27.1	27.4	64.4
2. R. K. ♀, 28	10/28/26	Alcohol	46.0	320 500	800	1250	300	525	621	423 500	860	1250	15.0	19.9	19.1
3. T. S. ♂, 30	11/27/26	Alcohol	77.0	320 320	500 320	320 200	928 1562	1702 1257	778 804	390 190	295 222	430 380	24.5	82.8	26.3
4. B. M. ♂, 68	11/27/26	Alcohol	23.2	50 320	500 200	800	2418 2404	1774 1310	1842	120 350	1425 940	5300	6.7	53.9	29.8
5. K. K. ♂, 44	12/21/26	Alcohol	92.5	1250 800	1250 800	2000	1064 694	1094 795	1432	4050 2650	1390 596	5000	110.8	91.4	327.2
6. Y. S. ♂, 43	11/13/26	Alcohol	101.0	0 5	5 5	5 2	51 59	64 13	146 73	70 506	872 228	280 340	0.42	8.6	3.5
	11/24/26	25% magnesium sulphate, 50 cc.	111.5	0 8	20 20	0 0	0 29	47 42	3 45	2 20	135 150	100 180	0.69	2.0	6.2
	11/26/26	Ether, 2 cc.	101.5	5 5	5 20	5	18 34	1 23	6	10 19	11 17	17	0.46	2.3	1.7
	12/10/26	Alcohol	156.0	16 10	5 5	0 2.5	59 82	90 84	121 125	25 23	22 21	14 19	1.24	13.6	3.5
	12/15/26	Alcohol, insulin, 10 units hypodermically	141.5	0 5	0 5	—	120 64	61 31	—	17 23	19 25	—	0.50	7.9	3.2
	1/16/27	Alcohol	109.5	0	5	5	23 60	39	71	27 10	13	25	0.38	6.5	2.7
	1/25/27	0.2% hydrochloric acid, 30 cc.	176.5	5	0	5	59	104	58	23	12	18	0.81	11.0	3.7
	7/20/27	No	96.0	10	0	0	15	4	11	8	4	3	0.28	1.1	....
7. K. K. ♂, 34	1/ 8/27	Alcohol	118.5	200 200	500 500	500 500	408	1027 1025	746 558	238 220	780 570	1904 632	42.2	58.2	73.6
8. S. S. ♂, 44	2/ 8/27	Water	159.0	500	500	500	1706	1085	1663	1125	1690	1560	79.5	233.4	245.3
9. K. S. ♂, 72	3/18/27	No	36.0	100 0	100 320	200	379 92	634 611	249	280 408	1260 2024	588	4.9	12.8	26.4
	3/20/27	Insulin, 15 units hypodermically	59.0	0	100	320	175	454	295	—	145	435	7.4	16.7	31.8
10. S. K. ♂, 49	4/13/27	Water	122.0	320	500	800	2083	2029	2101	104	210	984	67.7	253.3	58.2
11. K. S. ♂, 36	4/20/27	Water	154.5	500	500	500	1253	1675	1353	1204	1357	2544	66.6	218.7	278.0
12. Y. T. ♀, 60	5/31/27	No	59.5	320	320	320	1091	1207	1030	139	230	330	18.9	68.2	12.6
13. S. T. ♂, 33	6/ 1/27	Water	80.0	60	60	80	431	384	255	138	48	60	5.4	28.4	6.7
	6/17/27	Water	76.0	50	40	60	377	298	377	258	100	85	3.8	26.6	10.8
14. K. K. ♂, 69	6/10/27	Water	70.5	10	320	200	208	439	551	66	25	14	13.6	29.4	2.3
15. S. O. ♀, 44	6/15/27	No	55.6	10	200	10	43	373	423	284	960	320	6.1	17.0	34.9
	7/ 2/27	No	42.3	160	160	400	867	1360	990	804	915	1806	12.1	43.7	50.4
16. S. N. ♀, 31	6/19/27	No	66.0	200 500	200 0	0 200	554 936	395 56	113 511	1640 1190	546 310	200 2400	24.1	60.3	242.1
17. T. D. ♂, 36	6/22/27	No	70.5	200	500	500	510	900	1084	140	200	480	32.2	68.6	27.3
18. R. S. ♂, 59	9/ 9/27	Water	85.0	100	50	250	1054	854	1405	32	54	198	10.7	93.0	6.6
	9/30/27	Water	74.9	100	0	250	768	592	1382	148	87	140	15.9	95.9	16.6
19. F. I. ♂, 42	9/23/27	Water	102.0	100	250	100	402	2187	930	115	100	465	15.2	93.0	18.0
20. K. I. ♂, 46	9/27/27	Water	106.0	500	1250	1250	2273	2313	2442	468	1130	1550	107.0	249.9	117.9
21. M. S. ♀, 45	11/ 4/27	Water	63.0	200	0	320	1290	890	1538	275	85	400	14.1	84.3	18.9
† T. O. ♂, 45	11/19/26	Alcohol	34.5	320	320	—	901	931	—	280	400	—	10.9	26.4	10.5

* In this table, ♂ indicates male; ♀, female.

† Cancer of the pancreas.

‡ The cases, in which two degrees of enzymatic activity are shown, mean that every half hour collections were estimated separately.

¶ Alcohol, 10% solution, 30 cc.; water, 30 cc.

Lipase in 3 Hours, Klee Unit	Bile Pigment in 3 Hours, Mg.	Fasting Blood Sugar, per Cent	Highest Blood Sugar During the Course, per Cent	Urinary Sugar, per Cent	Highest Urinary Sugar During the Course, per Cent	Diacetic Acid#	Severity of the Disease	Duration in Years	Weight in Kg.	Diet§	Boiled Rice, Gm.	Calories per Kg.	Comment
58.6	3.2	0.106	0.531	—	8.0	+	Severe	1	48.5	Restricted	0	33.0	
64.4	5.8												
19.1	1.3	0.160	0.268	—	7.9	—	Severe	1	36.0	Restricted	90	35.5	
26.3	4.2	0.114	0.204	—	7.7	(++) —	Severe	1	51.7	Restricted	240	37.3	
29.8	0.4	0.100	0.440	—	6.3	(+++) —	Severe	11	53.8	Restricted	150	20.0	
327.9	15.9	0.164	0.381	2.0	5.6	—	Severe	5	41.0	Free	Plenty	....	+ Retinitis diabetica, nephritis, neuralgia
3.5	9.2	0.150	0.306	—	2.9	(++) —	Severe	1	58.2	Restricted	180	38.0	+ Cholecystitis
6.2	6.1	.....	.....	—	....	..	.....	....	....	Restricted	180	38.0	
1.7	6.9	.....	.....	—	....	..	.....	....	....	Restricted	180	38.0	
3.5	13.2	...	.....	0.6	....	..	.....	....	....	Restricted	180	38.0	
3.2	13.6	0.141	.....	—	....	..	.....	....	....	Restricted	250	40.0	
2.7	13.1	.....	.....	..	....	..	.....	....	....	Restricted	250	40.0	
3.7	6.4	.....	.....	..	....	..	.....	....	61.5	Restricted	250	40.0	
...	32.1	0.227	.....	—	....	..	.....	....	....	Restricted	250	40.0	
75.6	11.5	.....	0.195	3.1	3.9	—	Severe	0.5	49.1	Free	Plenty		
245.3	39.3	0.265	0.561	5.6	9.8	(+++) —	Severe	0.3	46.6	Free	Plenty	Ca. 35.0	+ Jaundice
26.4	6.0	0.227	0.510	4.1	8.5	—	Severe	0.8	43.5	Free	Plenty	32.0	
37.8	11.5												
58.2	11.5	0.196	0.315	2.5	6.7	—	Severe	8	....	Free	...	20-30.0	+ Pulmonary tuberculosis
278.6	18.3	0.104	0.196	—	10.5	—	Mild	1	54.7	Restricted	480	31.8	
12.6	6.8	0.150	0.415	—	5.0	—	Severe	2	30.4	Restricted	240	19.0	Catarrhal jaundice in 12 years; + pulmonary tuberculosis, exophthalmic goiter
6.7	1.3	0.110	0.220	—	4.6	—	Mild	Ca. 3	47.5	Free	Plenty	....	+ Exophthalmic goiter; periodical paralysis
10.8	0.2												
2.3	7.9	0.202	0.564	—	7.7	+	Severe	0.5	38.7	Restricted	60	38.0	
34.9	0.5	0.123	0.191	—	4.8	—	Mediocre	0.2	41.1	Restricted	300	40.5	+ Essential thrombopenia
50.4	3.5								41.0	Restricted	450	45.8	
202.1	19.9	0.311	0.498	9.9	13.0	—	Severe	1	27.5	Free	810	51.9	
27.3	18.7	0.315	0.440	6.5	9.7	(++) ++ (+++)	Severe	2	35.1	Free	780	Ca. 35.7	
6.6	9.6	0.180	.....	..	....	—	Mild	....	44.4	Free	Plenty	Ca. 20.0	+ Nephrocirrhosis, arteriosclerosis
16.6	14.8												
18.0	4.8	0.097	0.225	—	1.9	—	Mild	1	53.8	Restricted	600	44.3	
117.9	41.2	0.085	0.202	—	0.4	—	Mild	0.5	42.7	Restricted	900	35.4	Cholelithiasis 36 yrs.
18.9	13.6	0.134	0.293	—	5.7	—	Mediocre	5	49.5	Free	Plenty	Ca. 28.0	+ Pulmonary tuberculosis
30.5	2.8												

The marks in the brackets show that the diacetic acid reaction became positive sometime during the course of observation.

§ Restricted diet, in addition to rice, consisted of foods poor in carbohydrates such as eggs, beef, calf, fowl, fish, butter, cabbage, spinach, milk, tofu, tofukara and aburagé so that the amount of the rice may be seen as the measure of carbohydrate permitted.

under the arch of the left rib inside of the nipple line, so that we decided to try an exploratory laparotomy. On December 1, operation was performed by Professor Shioda, who found a cancer the size of a goose egg at the tail of the pancreas.

In this case, there was a disturbance of the external secretion of the pancreas, while the internal secretion was normal.

The foregoing cases show a representative disturbance of the pancreatic function. In the first case (case 6), there was a severe disturbance of both the internal and the external secretion, which showed that there was general involvement of the pancreas. In the second case (case 10), there was a severe disturbance of the internal secretion while the external secretion was normal, and the autopsy proved that the acinar cells remained almost intact while the insular cells were extremely atrophied. In the third case (cancer of the pancreas), the internal secretion was still sufficient to maintain the normal regulation of metabolism of sugar, while the external secretion was greatly diminished. Any functional disturbance of the pancreas might be grouped with one of these three forms, between which there are numerous transitional types.

Insulin usually causes active external secretion of the pancreas, increasing both the amount and the enzymatic activity when marked hypoglycemia develops. In two cases of severe diabetes (cases 6 and 9) with severe disturbance of the external secretion, we found almost no increase in one case, and only a slight increase in another case. Perhaps the structural alterations had already progressed so far that the cells which were still active were too few to react to stimulation.

COMMENT

In view of the foregoing observations, it is interesting to discuss the significance of the results obtained by our three hour method of calculating the total enzymatic efficiency. As already noted, more than one half of the cases (about 70 per cent) showed a diminution in the total efficiency of one or more of the pancreatic enzymes; the percentage of abnormality of the enzymatic activity was somewhat less (about one-half). The deviation of abnormalities in these two standards depends mainly on the fact that the duodenal return was small in some cases. It is possible that in some cases the enzymatic activity may be high when the secretion is scanty. This has been proved by our three hour method. The disturbance in the pancreatic function is manifest by diminution either of the enzymatic activity or of the amount of pancreatic juice, or of both. The method in which only the enzymatic activity is used to determine the efficiency of the pancreatic function does not include the two latter factors. On the other hand, it is also possible for a profuse secretion of the pancreas to be diluted by saliva, gastric juice and biliary secretion so that the enzymatic activity is relatively low. Jones, Castle,

Mulholland and Bailey noted the striking fact that the amylolytic activity was apparently diminished in only 9 per cent of the cases, whereas the proteolytic activity and the lipolytic activity showed definite reductions below the minimum normal level in over a third of the cases. The same striking fact was confirmed in our cases, amylolytic efficiency being diminished in only one third of the cases, whereas proteolytic and lipolytic efficiency showed reductions below the minimum normal level in over one half of the cases. Just why there should be a dissociation of these ferment actions would be extremely interesting to know; at present, however, we cannot offer a reasonable explanation. At least this disturbance cannot be attributed to the improper digestion of fat and protein in diabetes mellitus. In other conditions than diabetes, we could also find the same striking feature when disturbances of the enzymatic activity occurred. It is definitely proved that amylolytic activity is usually maintained with more extraordinary tenacity than the other two ferments.

That the severity of the diabetes does not necessarily run parallel to the degree of disturbance of the external secretion has already been mentioned. Some cases showed severe disturbance of both the internal and the external secretion of the pancreas, whereas others showed marked disturbance only of the internal secretion while the external secretion remained normal. There are also diseases in which the internal secretion is sufficient to maintain the normal regulation of metabolism of sugar, whereas the external secretion is markedly disturbed. Representative cases of these three forms are described in the foregoing case reports.

It is well known that marked undernutrition, with the resulting loss of weight, is accompanied by changes in the size and function of the pancreas. The majority of the patients included in this series, however, were not extremely emaciated and previous to the examination ingested over 30 calories per kilogram of body weight per day. The lowest figures for enzymatic activity were not necessarily found in patients who were strikingly underweight. In this connection, we agree with the observations of Jones and his co-workers, who also emphasized a marked increase in the elimination of the bile pigment in diabetes mellitus. Unfortunately, as far as the elimination of bilirubin was concerned, we could not confirm these data.

Jones and his co-workers noted that 19 per cent of their patients showed the characteristic symptoms of cholelithiasis. In our twenty-one cases, we could confirm a history of jaundice in four cases (19 per cent); in two of the cases (cases 12 and 20) cholecystitis or cholelithiasis developed a long time before the diabetes occurred; in one case (case 8), cholelithiasis and diabetes were associated and in another (case 6) the cholecystitis apparently appeared during the course of the diabetes.

Considering the historical data carefully, we hesitate at present to accept the etiologic rôle of gallbladder disease in these four cases.

Two patients in the series had a history of exophthalmic goiter; one patient (case 12) showed scarcely any symptoms of this disease when examined, whereas another (case 13) showed typical and severe symptoms of exophthalmic goiter, accompanied by periodic paralysis. The latter case is especially interesting. The glycosuria showed the highest percentage noted for thyrogenic glycosuria (highest urinary sugar, 4.6 per hundred cubic centimeters). It is well known that periodic paralysis is often accompanied by glycosuria and is considered by some authors (Lundborg, Shinosaki and others) as the manifestation of involvement of the parathyroid gland (hyperfunction). On the other hand, in exophthalmic goiter a special anatomic change in the pancreas, in both the acinous and the insular tissues, is noted. In this case, therefore, it seems difficult to decide whether the disturbance in the regulation sugar metabolism might be attributed to the pluriglandular involvement or to the pancreatic damage. The activity as well as the efficiency of the three pancreatic ferments, however, showed a marked decrease, so that the disturbance seemed to be due mainly to a general involvement of the pancreas associated with pluriglandular disease.

It is striking that the older patients showed almost all abnormalities of enzymatic efficiency of one or more of the enzymes. It is probable that some serious damage to both the insular and acinous cells (fibrosis and cellular degeneration or sclerosis) was the cause of the abnormalities in these cases.

SUMMARY

1. An unselected group of twenty-one diabetic patients was examined according to our newly devised method for evidence of alteration in the pancreatic activity. The total proteolytic efficiency as determined in 67 per cent of the three hour specimens showed amylolytic efficiency in 33 per cent and lipolytic efficiency in 57 per cent, values below our minimal normal limits. The efficiency of the three enzymes was within normal limits in 29 per cent of the cases; in 24 per cent the activity of all the enzymes was abnormally low. From the enzymatic activity the proteolytic activity was estimated in 43 per cent of the cases, the amylolytic activity in 20 per cent and the lipolytic activity in 43 per cent; the values were below our minimal normal limits. In 48 per cent of the cases, the activity of three enzymes proved to be within normal limits and in 14 per cent, abnormally low. The deviation of abnormalities in these two standards depends mainly on the fact that the amount of the duodenal return was scanty in some cases. The disturbance of the pancreatic function manifests itself in the diminution either of the enzymatic activity or of the amount of the pancreatic juice or of both. The method

in which only the enzymatic activity is used as a measurement of the pancreatic function does not take into consideration diminution in the secretion of the pancreatic juice or that both the pancreatic juice and the enzymatic activity may be decreased. The greatest alterations in enzymatic efficiency as well as activity were noted in the proteolytic and lipolytic ferments.

2. The severity of the diabetes is not necessarily parallel with the degree of disturbance in the external secretion. Some cases showed severe disturbance in both the internal and the external secretion of the pancreas, whereas others showed a marked disturbance only in the internal secretion, while the external secretion remained normal. There are also diseases in which the internal secretion of the pancreas is sufficient to maintain the normal regulation of metabolism of sugar, whereas the external secretion is markedly disturbed. Representative cases of these three types are described in detail.

3. Old patients showed almost all abnormalities of the enzymatic efficiency of one or more of the enzymes. It is likely that some serious damage to both the insular and acinous cells causes the abnormalities in these cases.

THE PREVENTION OF EXPERIMENTAL EXUDATES BY THE PARATHYROID HORMONE (COLLIP)*

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The view is commonly held that calcium salts inhibit the formation of effusions. The literature dealing with the experimental work on this subject seems to indicate that calcium is extremely effective for that purpose. It has not proved so in clinical practice in the manner in which the calcium salts are generally given. In a previous paper,[1] I described experiments that confirm the view that the calcium salts inhibit the formation of experimental exudates and pointed out some of the limitations that might readily vitiate the clinical usefulness of this antagonism. From that study, it appeared evident that the absolute inhibitory effect of the calcium salts is rather limited; that it depends on the dose of calcium and the intensity of the irritation; that an extremely large dose of calcium is necessary to inhibit the effects of moderate irritation, and that the effect of more intense irritation is practically uninfluenced even by fatal doses of calcium.

It was suggested that the failure to obtain more satisfactory results with the use of calcium salts in the prevention of effusions in man might be due, in part, to insufficient doses of the latter, and the difficulty of producing sufficiently persistent hypercalcemia with calcium salts. The parathyroid hormone produces hypercalcemia of considerable duration in normal animals.[2] A number of reports have appeared,[3] which show that the parathyroid hormone produces a diuresis and loss of fluid in certain patients with edema. The present study was undertaken to determine if the parathyroid hormone will prevent the formation of experimental effusions.

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1. Gold, Harry: On the Prevention of Experimental Effusions by Calcium Salts, J. Pharmacol. & Exper. Therap., to be published.

2. Collip, J. B.: The Parathyroid Glands, Medicine **5**:1 (Feb.) 1926.

3. Davidson, J. R.: A Case of Adolescent Myxedema, Accompanied by Tetany of Parathyroid Origin, Treated with Collip's Parathyroid Extract, Canad. M. A. J. **15**:803 (Aug.) 1925. Mason, E. H.: A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract, ibid. **16**:538 (May) 1926. Meakins, J. C.: Reaction of Chronic Nephrosis to Thyroid and Parathyroid Medication, J. A. M. A. **89**:149 (July 9) 1927. McCann, W. S.: Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, ibid. **90**:249 (Jan.) 1928.

EXPERIMENTAL WORK

Sixteen experiments were performed on dogs. The results are given in the accompanying table. Pleural effusions were produced by the introduction of an irritant (solution of copper sulphate) into the pleural cavity by means of a pleural cannula. About twenty-four hours later, the animal was

Effect of Parathyroid Hormone on Effusions Produced by Injection of Solution of Copper Sulphate into the Pleural Cavity

Number	Weight of Dog in Kg.	Copper Sulphate: Dose in Cc.	Copper Sulphate: Percentage of Solution	Interval in Hours Following Injection of Solution of Copper Sulphate	Cubic Centimeters of Fluid in Pleural Cavity	Dose of Hormone in Units	Remarks
1	5.40	1	1	24	2	...	
2	6.50	1	1	24	2	...	
3	9.30	1	1	20	90	...	
4	8.54	2	1	20	115	...	
5	8.68	2	1	29	150	...	
6	4.96	2	1	20	151	...	
7	8.30	1	1	22	170	...	
1	6.38	2	1	24	0	150	Hormone in 3 doses of 50 units each; first dose 5 hours before injection of solution of copper sulphate; nausea
2	9.00	1	1	20	0	200	Hormone in 4 doses of 50 units each; first dose 15 hours before injection of solution of copper sulphate; animal was depressed and vomited
3	8.60	1	1	22	0	100	Hormone in 2 doses of 50 units each; first dose 13 hours before injection of solution of copper sulphate; vomiting; diarrhea; serum calcium, 16.5 mg.; animal appeared normal the following morning
4	6.60	1	1	24	0	50	Hormone in 1 dose 10 hours before injection of solution of copper sulphate; slight depression; serum calcium, 19.4 mg.; appeared normal the following morning
5	4.82	1	1	24	25	150	Hormone in 3 doses of 50 units each; first dose 5 hours before injection of solution of copper sulphate; animal normal
6	10.94	2	1	20	26	150	Hormone in 2 doses; first 100 units 15 hours before injection of solution of copper sulphate; vomited; otherwise normal; pneumonia after injection of solution of copper sulphate; serum calcium, 18 mg.
7	5.72	2	1	20	30	200	Hormone in 3 doses of 100, 50 and 50 units; first 100 units 14 hours before injection of solution of copper sulphate; vomited; animal normal the following morning
8	3.50	1	1	44	44	50	Hormone in 1 dose 4 hours before injection of solution of copper sulphate; animal normal
9	7.30	2	1	21	110	100	Hormone in 2 doses of 50 units each; first dose 14 hours before injection of solution of copper sulphate; normal; serum calcium, 12.5 mg.

anesthetized, the chest was opened and the pleural fluid was removed and measured. Seven animals were used for control experiments. In these, there was scarcely any external evidence of disturbance, even when the pleural cavity contained as much as 170 cc. of exudate. The remaining nine dogs received the parathyroid hormone prior to the injection of the irritant. The hormone was generally given subcutaneously in several doses at intervals of about

two to four hours, the first dose being administered from four to fifteen hours preceding the injection of the copper sulphate solution into the pleural cavity. Some animals showed evidence of the toxic effects of the hormone, such as nausea, vomiting, diarrhea and depression; the others appeared quite normal. At the time of the intrapleural injection, the blood calcium was determined in four cases. By the method of Clark and Collip,[4] the serum calcium was found to range from 12.5 to 19.4 mg. per hundred cubic centimeters of blood.

COMMENT

The results, as seen in the table, indicate that the parathyroid hormone (Collip), given subcutaneously, diminishes or prevents pleural effusions following the intrapleural injection of an irritant (solution of copper sulphate). In the dog, it appears that considerable hypercalcemia is necessary, because the animal (number 9) that had a relatively low serum calcium behaved practically the same as the normal control animal in response to the irritation.

The observation that certain doses of the parathyroid hormone inhibit experimental exudates produced by a given kind and degree of irritation has interesting clinical possibilities. To what extent it will prove applicable for the prevention of clinical effusions remains to be determined by direct observations. Its usefulness will almost certainly be limited by such factors as the cause of the effusion, the intensity of the irritation, the degree to which the hormone will produce hypercalcemia in man without toxic symptoms and the degree of hypercalcemia necessary in man to impair the passage of fluid from the circulation into the tissues or body cavities.

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4. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification. J. Biol. Chem. **63**:461 (March) 1925.

CONTINUED ADMINISTRATION OF IODIDE AND OTHER SALTS

COMPARATIVE EFFECTS ON WEIGHT AND GROWTH OF THE BODY *

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The objections that have been raised against the prolonged administration of iodide in small doses are conspicuously unsupported by trustworthy evidence. The alleged deleterious effects are not clearly defined. The disturbing effects sometimes attributed to the use of iodide or iodine in the treatment for abnormalities of the thyroid may be due to the disease and not to the iodide. With the exception of the well known changes in the thyroid gland during hyperplasia and in cases of simple goiter and certain changes in the metabolism, important alterations in other organs and functions as a result of small doses of iodide have not been demonstrated. Marine's [1] statistical studies of clinical data indicate the lack of evidence of the alleged deleterious effects of iodide, and recently Read, Walker and McKenney [2] failed to demonstrate any effects on the pulse rate in human subjects observed during relatively short periods. Clinical data, however, could not reflect more than acute or periodic effects. A more critical test would be administration to animals over long periods under controlled conditions.

Changes in weight and growth of the body reflect the sum total of effects on functions of the body, so that objective evidence of this character would be important with reference to the iodide action under discussion. Although the results of such studies may not always be easy to interpret, yet if they are definite, they are suggestive, at least, and offer a point of departure for further study of specialized functions. Studies of the action of iodide over long periods along these lines have not been made previously. Clinically, they would be impracticable, but experimentally they are feasible with small animals. During the past four years, we have carried on such studies on rats and have observed the effects of iodide and other salts during from about one

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1. Marine: Medicine **6**: 127, 1927.

2. Read, Walker and McKenney: Proc. Soc. Exper. Biol. & Med. **24**: 322, 1927.

seventh to seven twelfths of the life span of these animals. The results obtained are interesting and sufficiently conclusive to warrant a report. The effects of the other salts were found to be in marked contrast to those of the iodide, thus emphasizing the distinctiveness of iodide, which was found to be beneficial and at least not harmful. Our results corroborate and correlate with interesting and important results from small doses of iodide reported in the literature of veterinary medicine.

METHOD

Four experiments were made with rats on a complete diet; one yearly during four successive years, from 1925 to 1928 inclusive, and one experiment with rats on a deficient diet. This provided ample opportunity for testing the validity of the results on different strains of rats, during different seasons, and for extending the comparisons to other salts. Only males were used, the groups for each experiment being from the same litter as much as possible. The number of animals in the different experiments ranged from three to five in a group for each salt and control; this is indicated in the accompanying charts. The groups on medicated food were always accompanied by control groups on untreated food. All experiments were started with young animals of equal weight (about 40 Gm.). The animals were weighed twice weekly throughout the experiments. The diet used was the modified adequate or complete diet of Osborne and Mendel, as used by Dr. Thomas Addis of the department of medicine,[3] 1 Kg. of which contained cornstarch, 440 Gm.; casein, 160 Gm.; lard, 140 Gm.; yeast, 100 Gm.; ground alfalfa, 20 Gm., cod liver oil, 109 cc., and the salt mixture of Osborne and Mendel,[4] 40 Gm.; this salt mixture contains about 0.0032 per cent of potassium iodide. The medicated foods were prepared by first dissolving the salt in a suitable small volume of water and then incorporating it with the food. The foods were dispensed in tared porcelain cups; water was provided liberally. The concentrations and doses of the salts varied.

Sodium iodide (dry) was used in a concentration of 0.01 per cent, which corresponded to about 1 mg. daily per rat or about 3.3 mg. daily per kilogram throughout the major part of the life of the rats. This dosage of iodide would correspond to about 0.23 Gm. (3½ grains) daily for an adult of 70 Kg. and might represent the daily amount used during a course of medication with iodide for the prevention of simple goiter, and that used in the treatment for toxic goiter and for chronic inflammations such as bronchitis, asthma and arthritis, but would be several times greater than the daily dose of iodide used in the form of iodized table salt.

The equivalent concentration of sodium sulphocyanate was 0.007 per cent, and of sodium bromide, 0.0054 per cent, the daily doses per rat of these salts being about 0.6 and 0.5 mg., respectively, and the daily doses per kilogram probably not over 2 mg. of each. These doses were chosen for comparison with iodide on a chemical basis. The median daily consumption of the sulphocyanate food was about 10 per cent less than that of the iodide, and of the bromide food about 2.2 per cent less.

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3. Dr. Addis provided generous supplies of this diet; the details of this and other diets and the methods of handling rats are given in the paper of MacKay and MacKay (Am. J. Physiol. **83**:179, 1927) from his laboratory.

4. Osborne and Mendel: J. Biol. Chem. **37**: 557, 1919.

Arsenic was used as the official Fowler's solution (liquor potasii arsenitis, U. S. P.), the concentration in food corresponding to 0.01 per cent of arsenous oxide; the daily dose per rat was about 0.76 mg. of arsenic trioxide estimated on the basis of a median consumption of 8 Gm. of food daily, and the daily dose per kilogram was not more than 2.5 mg., therefore, about three-quarters the dosage of iodide and nearly the equal of the doses of sulphocyanate and bromide. This dosage would be toxic for man, being the equivalent of 175 mg. or nearly 3 grains for a man weighing 70 Kg.; this dosage is known from Sollmann's work [5] to cause a definite loss of body weight in rats. The rats on arsenical food ate about 20 per cent less than those on the control and iodide foods. The dosage of manganese (as sulphate) in the experiment with the dietary for rickets was the same as that of arsenic.

Sodium borate was used in a concentration of 0.014 per cent which was ten times that necessary for plant growth found by Brenchley; [6] the daily dosage per rat was 1.12 mg. and the dose per kilogram per day about 3.7 mg., that is, nearly the same as that of iodide. This much or more would be ingested daily in preserved food. The consumption of borated food was 10 per cent less than that of iodized food, i.e., a median of 8.4 Gm. per day.

Thallium acetate was used in a concentration of 0.0014 per cent; the daily dose per rat was about 0.11 mg., or about 0.45 mg. per kilogram per day; the consumption of the thallium food was 16 per cent less than that of the control and iodized foods, and the animals died before maturity. This dose has been found by Buschke and Peiser [7] to cause definite effects in rats.

The results are presented in charts 1, 2, 3, 4 and 5, each of which gives the data on body weight and food consumption of an experiment. The curves represent median values at the end of each month, although weekly records in each experiment had been made throughout the work. Weekly records, however, were too unwieldy for reproduction and did not give more information than the monthly records. It will be understood that the values relating to changes in body weight, food consumption, etc., in the text all represent medians which were derived from tabulations. Charts 1, 2, 3 and 4 represent the results of experiments with salts in complete diet, and chart 5, in a rachitic diet.

IODIDE

Collectively, the experiments made show two main results with reference to iodide; (1) an increase in weight or growth of the body sometime during the course of ingestion of the iodized food as compared with the controls on unmedicated food; (2) in contrast with this effect of the iodide and generally with the controls, a reduction in the body weight and growth after medication with all other salts. These results hold for the majority, or four, of the five experiments made.

5. Sollmann: J. Pharm. & Exper. Therap. **18**: 43, 1921.

6. Brenchley: Inorganic Plant Poisons and Stimulants, ed. 2, London, Cambridge University Press, 1927.

7. Buschke and Peiser: Klin. Wchnschr. **5**: 977, 1926.

The increases caused by the iodide were variable, although during the course of an experiment they would be considerable for several months at a time. This can be seen from the accompanying charts. An approximate figure for all groups during the periods of observation made would be an increase of about 10 or 15 per cent. The importance of this figure lies in the facts that it represents an increase over considerable periods (months) and that the absolute increase would be important in practice during short or long periods, when transferred to man and larger organisms.

The actual values from the tabulations of our data on rats were as follows: In the majority, or three, of the four experiments made with the rats on complete diet, iodide increased the body weight from 6 to 25 per cent. An increase of 9 per cent was observed in the group of rats observed during twenty-one months (chart 1); a 6 per cent increase in the group observed during twelve months (chart 2), and an increase of 25 per cent in the group observed during five months (chart 4). The rats of each of these three groups which had received iodide ate the same amount of food as their controls on untreated food, namely, 10 Gm., 9.1 Gm., and 7 Gm., respectively. Apparently, therefore, the increases in body weight occurred independently of food consumption. Only one group of rats (chart 3) showed a loss of 7 per cent in body weight during seven months' observation; but their daily food consumption was 6 per cent less than that of their controls. This suggests that the diminished food consumption caused the difference in response to iodide from that of the majority of the rats. These rats grew less because they ate less. The diminished eating indicated some abnormality. This is not ascribed to an abnormality of the appetite due to the iodide, because the appetites of the majority of the rats showing increases in weight (positive experiments) were not affected.

Iodide in Rats on Deficient Diet.—Iodide was compared with arsenic and manganese in rats on the diet of Sherman and Pappenheimer [8] used for the production of experimental rickets, in connection with some other experiments. The results were interesting, because the iodide showed the usual difference from arsenic and also a difference from manganese. The iodide exerted a beneficial effect on growth and duration of life, while the rats receiving arsenic and manganese showed greater losses of weight and earlier deaths than the rats given iodide and the control rats. Chart 5 illustrates the course of events in these rats.

Experiments with other deficient diets were not made because of the erratic results obtained. The only agent observed to have bene-

8. Sherman and Pappenheimer: Proc. Soc. Exper. Biol. & Med. **18**:193, 1921.

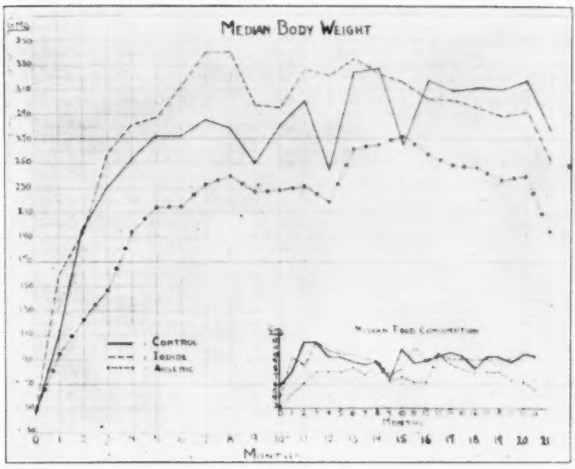

Chart 1.—Iodide and arsenic in rats on complete diet; three rats to a group (experiment 1). In all the charts, control rats were on the same but unmedicated diet.

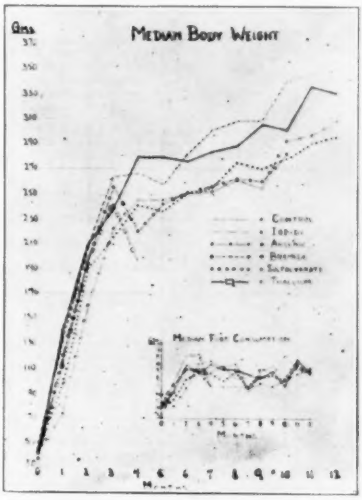

Chart 2.—Iodide, arsenic, bromide, sulphocyanate and thallium in rats on complete diet; five rats to a group (experiment 2).

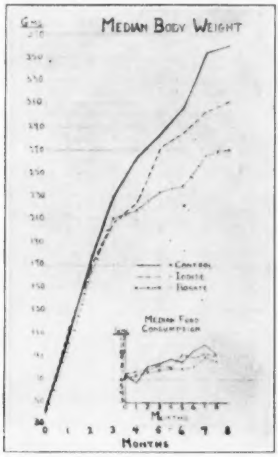

Chart 3.—Iodide and borate in rats on complete diet; five rats to a group (experiment 3).

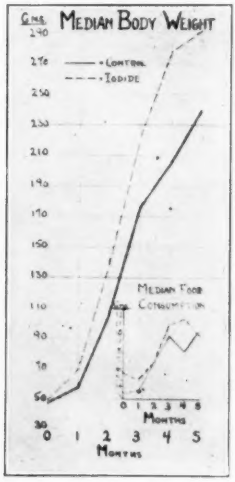

Chart 4.—Iodide in rats on complete diet; four rats to a group (experiment 4).

ficial effects in rats on a growth-deficiency diet was butylamine in 0.01 per cent concentration added to the food. This amine also caused an occasional spectacular recovery when an injection of it was made into pigeons which were moribund as a result of a polyneuritic diet (polished rice). The variable mortality, the intervention of infections, etc., in animals on deficiency diets made it difficult to interpret the results. In any case the results on complete dietary are of greater importance in the present connection.

It may be concluded that iodide in continued small daily doses in food over long periods causes moderate though variable increases in body weight, and that it does not impair growth except occasionally when the food consumption may be less. In contrast with these actions

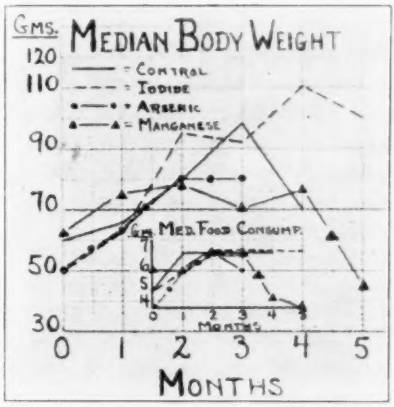

Chart 5.—Iodide, arsenic and manganese in rats on rachitic dietary; three rats to a group (experiment 5). The controls were on an unmedicated rachitic diet.

of the iodide were the detrimental effects of a number of other salts, which served as further controls on the iodide since they were produced simultaneously in the different groups of rats.

OTHER SALTS

The results with the other salts were sufficiently interesting to be worthy of a separate and brief summary, according to each salt. The doses were given in the first part of the paper.

Sulphocyanate.—In many respects, sulphocyanate is chemically and pharmacologically close to iodide, but the effects on body weight were the opposite, causing a reduction of 10 per cent. The daily consumption of food was also reduced 10 per cent, and this probably explains

the corresponding loss of body weight, just as in the case of the iodide in experiment 3, which has already been discussed.

Arsenic.—Used as the official liquor potassii arsenitis (Fowler's solution) during twenty-one months in experiment 1 and during twelve months in experiment 2, arsenic caused losses in body weight of 20 and 10 per cent, respectively; the daily food consumption was reduced about 22 per cent (experiment 1) and 10 per cent (experiment 2). Here, again, the diminished food consumption explains the retarded growth of the animals. Two of the rats in experiment 2 died at the end of four months and ten months. Our results with arsenic generally confirm those of Sollmann [5] on chronic intoxication with arsenic trioxide, their main importance in the present connection being as controls of the general technic and response of the rats used alongside of their partners receiving iodide, thus indicating the correctness of our results with the latter.

Borate.—Used as sodium borate during seven months, this salt caused a median loss of 17 per cent in body weight. The daily food consumption was reduced somewhat less, i.e., 10 per cent., but would practically account for the loss of growth. Rats of the same litter receiving iodide at the same time showed losses of only 7 per cent in body weight, and only 6 per cent in food consumption. This indicates that the borate was more detrimental than the iodide, the latter being more favorable to growth, under the otherwise unfavorable circumstances of reduced food consumption by the same group of rats. The results with the borate confirm what is known from other sources about the detrimental effects on health from continued use of borated food.

Thallium.—The most toxic of all the salts was thallium. All five rats died suddenly at the end of four months, and all had showed the typical depilatory action at the end of six weeks, after the beginning of the administration. When one considers the severe effects produced, the changes in body weight and food consumption appeared proportionately small, but there may have been greater effects on specific functions or organs. Body weight was decreased 13 per cent and food consumption 16 per cent. Here, again, the lowered food intake could explain the nearly corresponding decrease in body weight or deficient growth. The sudden fatal termination was rather striking. The general appearance of the rats just before death was good, but the morbidity may have been greater than could be judged from external appearances. The depilatory and general injurious actions claimed by Buschke and Peiser [7] and others are fully confirmed. As a hair-remover, the drug should be used cautiously, if at all. The results obtained with thallium served the usefulness of still another control on

the iodide action, for the rats of the same litter treated with iodide showed an increase of 6 per cent in body weight.

Bromide.—Sodium bromide caused a loss of 11 per cent in body weight but only 2.2 per cent in food consumption, suggesting that the diminished food intake was not wholly responsible for the greater loss in body weight. This haloid acted as a control for the iodide from the chemical standpoint. Pharmacologically, it acts differently. Whether the small daily doses employed could saturate the brain sufficiently so as to give some degree of depression (hypnotic action) is not known. The experiment lasted seven months, a period which is certainly long enough for saturation. However, lethargy or narcosis in the animals was not observed at any time.

It may be concluded that the chemically or pharmacologically related ions, sulphocyanate and bromide, in small continued doses corresponding to those of iodide cause opposite effects from iodide on body weight and growth of healthy rats on a complete diet, namely, a depression, an effect also caused by small, continued doses of arsenic, borate and thallium, and also by manganese in rats on a deficient diet. Thus, the action of these salts is in strong contrast to that of the iodide.

COMMENT

The results that we obtained with small doses of iodide agree with the augmentor effects on growth and correlated functions of similar doses observed by others. Our results corroborate those of Mačela [9] on rats. Mačela found that daily doses of 0.2 mg. of sodium iodide added to food caused faster gains in body weight than among controls; the treated rats also showed a more rapid sexual development. The results agree with those of Evvard and Culbertson [10] on pigs receiving food containing 0.01 per cent potassium iodide; the pigs receiving medicated food gained an average daily increase of 10 per cent in body weight, thus indicating the economic possibilities of iodide for feeding livestock. Increased growth of yeast treated with low concentrations of iodide (from 0.001 to 0.5 per cent) has been reported by Scharrer and Schwartz.[11]

The results obtained correlate with the lasting depressant effects of small doses (from 0.5 to 10 mg.) of iodide on the metabolism of rats observed by Hildebrandt; [12] large doses gave the opposite effect. Depressant effects of small doses of iodide on metabolism in man

9. Mačela: Čas. lek. Česk. **64:** 1551, 1925.

10. Evvard and Culbertson: Research Bulletin of Iowa Agricultural Experiment Station **80:** 183, 1925.

11. Scharrer and Schwartz: Biochem. Ztschr. **187:** 159, 1927.

12. Hildebrandt: Arct. f. exper. Path. u. Pharmakol. **96:** 292, 1923.

have been reported by Loewy and Zondek [13] and by Neisser.[14] Hence, it would appear that the increased body weight resulting from the administration of small doses of iodide was the result of a retarded or depressed metabolism. Since the consumption of food was identical in our rats receiving iodide and the control rats, the increase in body weight was not due to more eating or a better appetite but to a direct action of the iodide on the tissues. Januschke [15] pointed to iodide as being both a sedative and a stimulant according to the dosage or concentration for different organisms or tissues, and asserted that small doses of iodide (0.5 Gm. twice daily) increase the body weight while larger doses decrease it. That large doses increase metabolism and reduce body weight has been adequately demonstrated. Recently, Grabfield [16] concluded from his extensive studies of iodide that the increased metabolism is mediated through the thyroid gland. There is no reason to invoke this mechanism for small doses of iodide in healthy subjects. Comparing bromide and chloride with iodide, all in large doses, Hesse [17] demonstrated the greatest increase in the metabolic rate of cats, rabbits and dogs with iodide; sulphocyanate did not increase the metabolic rate. Differences between the bromide and sulphocyanate ions were demonstrated also in our work. A more extensive discussion of the opposite metabolic actions of small and large doses of iodide will be found in a recent review by Bürgi.[18]

It is of interest to note that during the past three years a number of investigators [19] have reported the beneficial effects of small doses of iodide on the production of milk in cattle, a matter of some importance in child welfare. Daily doses of from 1.53 to 3.82 mg. in salt or feed given to cows or goats improved the quality and increased the quantity of milk; this milk increased the growth of young rats 20 per cent over the controls, although it was claimed to be practically free from the iodide ion; it was not harmful to infants. Likewise, pigs nursed by sows receiving iodized food attained a much greater body weight at the time of weaning than those of mothers which had not received medi-

13. Loewy and Zondek: Deutsche med. Wchnschr. **47:** 349, 1921.

14. Neisser: Berl. klin. Wchnschr. **57:** 461, 1920.

15. Januschke: Wein. med. Wchnschr. **76:** 1498, 1926.

16. Grabfield: Boston M. & S. J. **197:** 1121, 1927.

17. Hesse: Arch. f. exper. Path. u. Pharmakol. **102:** 63, 1924.

18. Bürgi: Heffter-Heubner: Handbuch f. exper. Pharmakol. **3:** 366, 1927.

19. Stiner: Schweiz. med. Wchnschr. **55:**670, 1925; **57:**846, 1927. Strobel and Scharrer: Biochem. Ztschr., **180:** 300, 1927. Scharrer and Schwaibold: Biochem. Ztschr. **180:** 307, 1927. Strobel, Scharrer and Schropp: Biochem. Ztschr. **180:** 313, 1927. Schwaibold and Scharrer: Biochem. Ztschr., **180:** 334, 1927. Scharrer: Ztschr. f. d. ges. exper. Med. **56:**677, 1927. Kieferle, Kettner, Zuler and Hanusch: Milchwirt, Fortschr. **4:**1, 1927. Maurer and St. Diez: Biochem. Ztschr. **182:** 291, 1927.

cation.[20] The increase in production of milk would appear to be intimately associated with the conservation of general metabolic processes, but whatever the mechanism, the collective results cited indicate that continued small doses of iodide are beneficial to the organism, thus emphasizing also the biologic rôle of this ion.

CONCLUSIONS

1. The continued administration of iodide in small daily doses in food over long periods (covering from about one seventh to seven twelfths of the span of life) to rats caused moderate though variable increases in weight and growth of the body in the majority of animals on complete dietary. The same tendency was indicated in rats on a deficiency diet.

2. The dosage of iodide employed corresponded to that which may be employed under clinical conditions, but was probably greater than that used as iodized table salt.

3. In contrast to the results obtained with iodide were those with sulphocyanate, bromide, arsenic, thallium and manganese, as controls, under the same conditions; these salts reduced body weight and growth, and arsenic and thallium caused fatalities.

4. The results obtained with the iodide corroborate and correlate with interesting and important results obtained with small doses of iodide reported in the literature of veterinary medicine.

5. Hence, there is no reason to believe from these experiments that the prolonged use of iodide in small doses under ordinary conditions is detrimental. On the contrary, the results along various lines indicate that it is beneficial. This would not apply to the continued use of iodide in specific conditions of the thyroid, or to large doses of the drug.

20. Weiser and Zaitschek: Biochem. Ztschr. **187:** 377, 1927.

THE INHERITANCE OF MIGRAINE*

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There are few maladies that cause in the aggregate as much suffering as migraine, and about which so little is known concerning either causes, mechanism, prevention or cure. By migraine I mean any headache beginning in early life, recurring regularly or irregularly over a long period of years, without a discoverable pathologic process and without materially affecting the general state of health; such headaches are predominantly frontal and unilateral and are accompanied by nausea and vomiting, soreness of the eyeballs and scalp and in the majority of persons at some time by flittering scotoma or other sensory symptoms. The hereditary nature of migraine, since it is the subject of this study, has been purposely left out of the definition just given, but any consideration of the subject will always show that, next to pain in the head during attacks, the history of similar attacks in parents and in other members of the family is its most constant feature.

Liveing [1] credited Tissot [2] with being the first to emphasize the hereditary factor in migraine, but, as Smith [3] pointed out, its familial occurrence had been the subject of comment since the beginning of the eighteenth century. Smith reviewed the gradual rise in the figures of parental history of migraine from 1858, when Symonds [4] reported that 44 per cent of migrainous persons gave a history of headache in one or both parents. During the next half century, Liveing, in 1873, reported 50 per cent; Henchen,[5] in 1881, reported 64 per cent; Moebius,[6] in 1894, reported 90 per cent and Auerbach,[7] in 1912, reported almost 100 per cent. In his own investigations, Smith found that when he could personally interview the parents of his migrainous patients, he always found migraine in them.

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* Read before the Joint Session of the Eugenics Research Association and the American Eugenics Society, New York, June 2, 1928.

1. Liveing, E.: Megrim, Sick Headache and Allied Disorders, London, J. & A. Churchill, 1873.

2. Tissot: Traite des Nerfs et de leur Maladies, Boyle's ed., 1834, p. 383.

3. Smith, Jens: Om Migraeneus Arveligheds forhold, Bibliot. f. Laeger, August, 1922, p. 310.

4. Symonds: Gulstonian Lectures, M. Times & Gaz. 1858, p. 498.

5. Henchen, S. E.: Studier oefver Hufondets Nevralgier, Upsala, 1881.

6. Moebius: Die Migraine, Vienna, 1903.

7. Auerbach, S.: Headache, translated by E. Playfair, London, Oxford University Press, 1913, p. 36.

Along with this clinical observation pointing toward the direct inheritance of migraine, a number of impressions that do not correspond at all with direct inheritance of any sort have become firmly fixed in the literature of migraine. The commonest of these discordant factors is the marked preponderence of women in the various series of case reports. However, a statistical study [8] of the sex ratio in migraine shows that men and women are affected in equal numbers, making it unnecessary to predicate any form of sex linkage.

A second erroneous clinical impression, often repeated, is that brain workers are more subject to migraine than those who work with their hands. A statistical study [9] of the occupations of 400 persons with migraine failed to show that occupation bore any relation to its incidence.

A third impression is that in passing from generation to generation, migraine may appear as, or come from, a number of other conditions, ranging all the way from cancer and diabetes through the psychoses to epilepsy. A statistical study [10] of 400 migrainous persons showed that psychoses, psychoneuroses and epilepsy were not any more frequent among migrainous than among nonmigrainous persons.

Up to the present time, few attempts have been made to correlate the observations on the familial occurrence of migraine with the laws of heredity originally discovered by Mendel.

In 1920, Buchanan [11] concluded that migraine is hereditary in accordance with Mendel's laws but did not consider the question of its dominance or recessiveness. His evidence is as follows: (*a*) in 100 families in which one parent was migrainous and which contained 631 children, 143 (22.66 per cent) had migraine; (*b*) in 17 families in which neither parent was migrainous and which contained 115 children, 30 (26 per cent) had migraine; this situation can be explained only on the assumption that migraine is recessive, and that all the parents in this group were heterozygous for migraine; (*c*) in three families in which both parents were migrainous and which contained fifteen children, all (100 per cent) had migraine. This group might represent matings of either pure dominants or pure recessives and does not give any evidence on the question of dominance. Part of Buchanan's evidence points to migraine as a recessive trait, and part of his data does not give evidence either way.

8. Allan, W., to be published.

9. Allan, W.: The Relation of Occupation to Migraine, J. Nerv. & Ment. Dis. **66**:131 (Aug.) 1927.

10. Allan, W.: The Neuropathic Taint in Migraine, Arch. Neurol. & Psychiat. **18**:587 (Oct.) 1927.

11. Buchanan, J. A.: The Mendelianism of Migraine, M. Rec. **98**:807 (Nov. 13) 1920.

In 1922, Smith [3] stated (*a*) that a hereditary trait should be more prevalent among siblings of the possessor of such a trait than in the general population. This would vary with the incidence of the trait in the general population. In the case of migraine, if one uses my figures of 60 per cent incidence, the trait should be found in 77.8 per cent of the siblings, if dominant, and in 78.7 per cent, if recessive. Thus it will be seen that the incidence of migraine in siblings in this study could be of value in showing the hereditary nature of the malady but not in differentiating between dominance and recessiveness. Smith found the incidence in 158 women to be 37, or 23.5 per cent, and the incidence among 133 siblings to be 61, or 45.8 per cent.

Smith further stated (*b*) that direct parental inheritance points toward a dominant trait, but this is doubtful evidence, as it will be seen from tables 1 and 2. There will be parental headache in 100 per cent of the instances if it is a dominant trait, or if headache is recessive, accepting the incidence as 60 per cent, there will still be parental head-

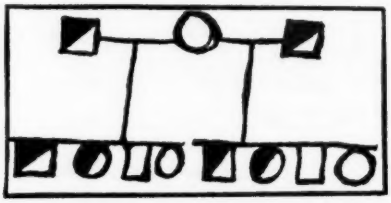

Fig. 1.—Inheritance of migraine. The white areas show migraine (recessive) and the black areas, normal (dominant).

ache in 95 per cent of the instances (in table 2), one fourth of matings 5, one half of 6, one half of 8, and 9 giving 60 per cent incidence; one fourth of 5 giving only 3, or 5 per cent, without parental headache.

Smith said (*c*) that the recurrence of headache in four or five successive generations points toward a dominant trait, but this is not always true, for with the incidence of migraine as high as it is, even though it were a recessive trait, 78 per cent of the matings among the general population would show migraine in both parents and children (table 2, matings 6, 8 and 9).

Smith said (*d*) that if a migrainous person marries twice, each mate being nonmigrainous yet both sets of children having migraine, this points toward a dominant trait. But if migraine is recessive and a migrainous person should marry two mates heterozygous for migraine, half of each set of children would have migraine. Under the known high incidence of migraine, this would be probable as well as possible.

Smith's evidence is largely for dominance, though partly (*b*, *c* and *d*) inconclusive. He concluded that migraine is a dominant trait that in some way is sex determined.

The present conception of hereditary traits, based on the original laws of Mendel, is that such traits may be inherited as unit characters—the tallness of garden peas, for example, with its opposite shortness being the only possibility, as in complete dominance blending of such opposed traits does not occur. Since the work of Wilson,[12] Morgan [13] and others, there has been a rational explanation of the physical basis of heredity in the packets of chromatin called genes which compose the chromosomes, one chromosome of each pair in any individual being derived from each parent. Thus if tall and short peas are crossed, their offspring will inherit tallness from one parent and shortness from the other, and as tallness is dominant in this cross all of this generation of hybrids will be tall. In the maturation of the germ cells in heterozygous individuals such traits segregate, half of the germ cells receiving

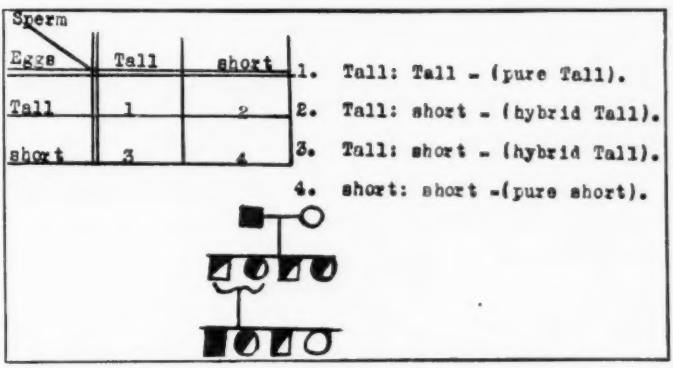

Fig. 2.—Crossing of hybrid peas, showing chance union of germ cells.

one trait, the other half the opposite trait. Thus, the germ cells of the hybrid peas would contain genes for tallness or for shortness in about equal numbers. When such hybrids are crossed the chance union of the germ cells results, as illustrated in figure 2.

If migraine is hereditary, the question of dominance or recessiveness is the first to arise. This is attacked first on the general aspect of the data, and later on a statistical basis. From a general consideration of the families, the answer is not immediately forthcoming, due to several facts. First, migraine is a subjective phenomenon which cannot be mechanically measured. Second, its allelomorph is not a definite character but is simply the absence of headache. There are headaches of many

12. Wilson, E. B.: The Cell In Development and Heredity, ed. 3, New York, The Macmillian Company, 1925.

13. Morgan, T. H.: The Theory of the Gene, New Haven, Yale University Press, 1926.

sorts, and in any series of headaches thought to be hereditary there will be some error in diagnosis. Thus the usual criteria of dominance and recessiveness—purity of the germ cells of the recessive type, absence of recessive offspring when one parent is homozygous dominant, etc.—are not practicable in this case. It is necessary to treat the data statistically, comparing the observed figures with the expected results and considering the character first as a dominant, then as a recessive.

To determine the incidence of migraine in the general adult population, 282 men taken consecutively were asked about headache and a positive history of migraine obtained in 57.4 per cent. In the same way, 62.6 per cent of 348 women gave a positive history of migraine. In view of the mild character and infrequence of attacks of migraine in some persons, this average incidence of 60 per cent will be somewhat below the real incidence.

It is evident that in dealing with a hereditary trait it is necessary to know the relative frequencies of the factors concerned and from these to calculate the relative occurrence of homozygous dominants, heterozygous dominants and recessives. Then, and only then may tables be constructed showing the statistical results to be expected in mass matings of various types. The frequencies of the factors concerned, if migraine is first considered as a dominant and then as a recessive and my figures of 60 per cent occurrence of migraine in the general population being used, are as folows:

If migraine is dominant,

Let M = gene for migraine
then m = gene for normal condition

And let p = frequency of M
and q = frequency of m

Then $p + q = 1$

The possible combinations of these factors are expressed by the equation $(p+q)^2=1$. From this, the following combinations are formed:

	M	m
	p	q
M	MM	Mm
p	p^2	pq
m	Mm	mm
q	pq	q^2

$p^2 + 2pq$ = migrainous persons
q^2 = nonmigrainous persons
$q = \sqrt{\text{nonmigrainous persons}}$

Substituting the figures that I have found for nonmigrainous persons, one has

$$q = \sqrt{.40} = 0.632$$
$$p = 1 - q = 0.368$$

Substituting values of p and q in the foregoing equations, one has

p^2 = Homozygous migrainous persons	13.5 per cent	(MM)
$2pq$ = Heterozygous migrainous persons	46.5 per cent	(Mm)
q^2 = Nonmigrainous persons	40.0 per cent	(mm)

Within the migrainous persons, there are the following relations:

Homozygous migrainous	22.5 per cent (MM)
Heterozygous migrainous	77.5 per cent (Mm)

If migraine is recessive,

Let M = gene for normal condition
then m = gene for migraine
And let p = frequency of M
and q = frequency for m
Then $p + q = 1$

The possible combinations of these factors are expressed by the equation $(p+q)^2=1$. From this, the following combinations are formed:

	M	m
	p	q
M	MM	Mm
p	p^2	pq
m	Mm	mm
q	pq	q^2

$p^2 + 2pq$ = nonmigrainous persons
q^2 = migrainous persons
$q = \sqrt{\text{migrainous persons}}$

Substituting the figures that I have found for migrainous persons, one has

$$q = \sqrt{.60} = 0.774$$
$$p = 1 - q = 0.226$$

Substituting values of p and q in the foregoing equations, one has

p^2 = Homozygous nonmigrainous persons	5.0 per cent	(MM)
$2pq$ = Heterozygous nonmigrainous persons	35.0 per cent	(Mm)
q^2 = Migrainous persons	60.0 per cent	(mm)

Within the nonmigrainous persons are the following relations:

Homozygous nonmigrainous,	12.5 per cent
Heterozygous nonmigrainous,	87.5 per cent

Migraine in the general population is represented in tables 1 and 2.

STATISTICAL REQUIREMENTS

If migraine is a true mendelian unit character, it will fulfill certain statistical requirements relative to its occurrence in parents, children and siblings. These requirements have been calculated on the basis of migraine as both a dominant and as a recessive, the frequencies derived in the foregoing tables being used. My figures are compared with the statistical requirements in each case.

1. When both parents have migraine, the percentage of migraine in the children should be, if dominant, 84.9 and if recessive, 100 (table 3). My figures are 83.3 per cent.

TABLE 1.—*Incidence in General Population If Migraine Is Dominant*

	MM .135	Mm .465	mm .400
MM .135	1 .018	2 .063	3 .054
Mm .465	4 .063	5 .216	6 .180
mm .400	7 .054	8 .180	9 .160

1. MM × MM — MM MM MM MM	1.8%
2. MM × Mm — MM MM Mm Mm	6.3
3. MM × mm — Mm Mm Mm Mm	5.4
4. Mm × MM — MM MM Mm Mm	6.3
5. Mm × Mm — MM Mm Mm mm	21.6
6. Mm × mm — Mm Mm mm mm	18.6
7. mm × MM — Mm Mm Mm Mm	5.4
8. mm × Mm — Mm Mm mm mm	18.6
9. mm × mm — mm mm mm mm	16.0
	100.0

TABLE 2.—*Incidence in General Population If Migraine Is Recessive*

	MM .05	Mm .35	mm .60
MM .05	1 .0025	2 .0175	3 .0300
Mm .35	4 .0175	5 .1225	6 .2100
mm .60	7 .0300	8 .2100	9 .3600

1. MM × MM — MM MM MM MM	0.25%
2. MM × Mm — MM MM Mm Mm	1.75
3. MM × mm — Mm Mm Mm Mm	3.00
4. Mm × MM — MM MM Mm Mm	1.75
5. Mm × Mm — MM Mm Mm mm	12.25
6. Mm × mm — Mm Mm mm mm	21.00
7. mm × MM — Mm Mm Mm Mm	3.00
8. mm × Mm — Mm Mm mm mm	21.00
9. mm × mm — mm mm mm mm	36.00
	100.00

TABLE 3.—*Incidence of Migraine When Both Parents Have It (Migraine Dominant)*

	MM 0.225	Mm 0.775
MM 0.225	1 0.051	2 0.174
Mm 0.775	3 0.174	4 0.601

		% MM	% Mm	% mm
1. MM MM MM MM	5.1%	5.1		
2. MM MM Mm Mm	17.4	8.7	8.7	
3. MM MM Mm Mm	17.4	8.7	8.7	
4. MM Mm Mm mm	60.1	15.0	30.0	15.0
		37.5	47.4	15.0
			84.9	

TABLE 4.—*Incidence of Migraine When One Parent Has It (Migraine Dominant)*

	MM 0.225	Mm 0.775		% Mm	% mm
				22.5	
mm 1.00	1 0.225	2 0.775	1. Mm Mm 22.5%	38.75	38.75
			2. Mm mm 77.5	61.25	38.75

TABLE 5.—*Incidence of Migraine When One Parent Has It (Migraine Recessive)*

	MM 0.125	Mm 0.875		% Mm	% mm
				12.5	
mm 1.00	1 0.125	2 0.875	1. Mm Mm 12.5%	43.7	43.7
			2. Mm mm 87.5	56.2	43.7

2. When only one parent has migraine, the percentage of migraine in the children should be, if dominant, 61.2 and if recessive, 43.7 (tables 4 and 5). My figures are 61.

3. When neither parent has migraine, the percentage of migraine in the children should be, if dominant, 0 and if recessive, 19.1 (table 6). My figures are 3.7 per cent.

4. There should be a history of migraine in one or both parents of migrainous children: if dominant, in 100 per cent (table 1), matings (1 to 8) and if recessive, in 95 per cent (table 7). My figures are 91.4 per cent.

TABLE 6.—*Incidence of Migraine When Neither Parent Has It (Migraine Recessive)*

	MM 0.125	Mm 0.875		% MM 1.6	% Mm	% mm
MM	1	2	1. MM MM MM MM 1.6%	10.9	10.9	
0.125	0.016	0.109	2. MM MM Mm Mm 10.9	19.1	38.3	19.1
			3. MM MM Mm Mm 10.9			
Mm	3	4	4. MM Mm Mm mm 76.6	31.6	49.2	19.1
0.875	0.109	0.766				

TABLE 7.—*Incidence of Migraine When One or Both Parents Have It (Recessive)*

Table 2, One half of matings 6 = 10.50
One half of matings 8 = 10.50
Matings 9 = 36.00

Total incidence 60 | 57.00 | 0.95

TABLE 8.—*Incidence of Migraine When Both Parents Have It (Dominant)*

Table 1, mating 1 = 1.8
Mating 2 = 6.3
Mating 4 = 6.3
Three fourths mating 5 = 16.2

Total incidence 60 | 30.6 | 0.51

TABLE 9.—*Incidence of Migraine When One Parent Has It (Dominant)*

Table 1, mating 3 = 5.4
One half of mating 6 = 9.3
Mating 7 = 5.4
One half of mating 8 = 9.3

Total incidence 60 | 29.4 | 0.49

TABLE 10.—*Incidence of Migraine When One Parent Has It (Recessive)*

Table 2, one half mating 6 = 10.50
One half mating 8 = 10.50

Total incidence 60 | 21.00 | 0.35

5. Both parents of migrainous children should have migraine: if dominant, in 51 per cent (table 8) and if recessive, in 60 per cent (in table 2); only in mating 9 are both parents migrainous=36 per cent of 60=60 per cent. My figures are 26 per cent.

6. Only one parent of the migrainous should have migraine: if dominant, in 49 per cent (table 9) and if recessive, in 35 per cent (table 10). My figures are 60 per cent.

7. Neither parent of migrainous children should have migraine: if dominant, in 0 per cent (table 1) and if recessive, in 5 per cent (table 2) one fourth of mating 5, 3 in 60=5 per cent. My figures are 8.6 per cent.

8. Siblings of migrainous persons should have migraine: if dominant, in 77.8 per cent (table 11) and if recessive, in 78.7 per cent (table 12). My figures are 67.2 per cent.

TABLE 11.—*Incidence in Siblings of Migrainous (Dominant)*

Table 1, mating 1 =	1.8	migrainous siblings	100% =	1.8
Mating 2 =	6.3	migrainous siblings	100% =	6.3
Mating 3 =	5.4	migrainous siblings	100% =	5.4
Mating 4 =	6.3	migrainous siblings	100% =	6.3
Three fourths of mating 5 =	16.2	migrainous siblings	75% =	12.2
One half of mating 6 =	9.3	migrainous siblings	50% =	4.65
Mating 7 =	5.4	migrainous siblings	100% =	5.4
One half of mating 8 =	9.3	migrainous siblings	50% =	4.65
Total incidence 60				46.70 | 77.8

TABLE 12.—*Incidence in Siblings of Migrainous (Recessive)*

Table 2, One fourth of mating 5 =	3.08	migrainous siblings	25% =	0.77
One half of mating 6 =	10.50	migrainous siblings	50% =	5.25
One half of mating 8 =	10.50	migrainous siblings	50% =	5.25
Mating 9 =	36.00	migrainous siblings	100% =	36.00
Total incidence 60				47.27 | 78.8

TABLE 13.—*Incidence in Siblings of Nonmigrainous (Dominant)*

Table 1, One fourth of mating 5 =	5.4,	with 75% migrainous	=	4.05
One half of mating 6 =	9.3,	with 50% migrainous	=	4.65
One half of mating 8 =	9.3,	with 50% migrainous	=	4.65
Total incidence 40				13.35 | 33.4

TABLE 14.—*Incidence in Siblings of Monmigrainous (Recessive)*

Table 2, Three fourths of mating 5 =	9.18,	with migrainous siblings	25% =	2.3
One half of mating 6 =	10.50,	with migrainous siblings	50% =	5.25
Mating 8 =	10.50,	with migrainous siblings	50% =	5.25
Total incidence 40				12.80 | 32

9. Siblings of the nonmigrainous should have migraine: if dominant, in 33.4 per cent (table 13) and if recessive, in 32 per cent (table 14). My figures are 11.5 per cent.

CLINICAL DATA

The statistics used here, except items 3 and 9, were taken from a review of 500 of my cases of migraine. The actual clinical data are as follows:

1. In 56 families in which both parents were migrainous and which contained 318 children, 240 had migraine, 48 did not and in 30 the history was not known or the children were too young, giving a positive figure of 83.3 per cent.

2. In 141 families in which one parent was migrainous and one not and which contained 750 children, 342 had migraine and 217 did not; in 191, the history was not known or the children were too young. This gives a positive figure of 61 per cent. In 99 families in which one parent was migrainous and the history of one unknown and which contained 517 children, 266 were migrainous, 153 were not and in 152 the history was not known. This gives a positive figure of 63.4 per cent. If one combines these two groups one has 240 families in which it was known that one parent had migraine. Of the 978 children about whom data were available, 62 per cent had migraine.

3. In 98 families in which neither one of the parents had migraine, containing 485 children, 18, or 3.7 per cent, had migraine.

4. A history of migraine in one or both parents was given in 349 (91.4 per cent) of 382 migrainous patients.

5. Data on both parents were obtained from 243 patients, and in 63 instances (26 per cent) both parents were said to have migraine.

6. A history of migraine in one parent but not in the other was given in 147 (60 per cent) of 243 migrainous patients.

7. A history of migraine in neither parent was given in 33 (8.6 per cent) of 382 migrainous patients.

8. In the families of 376 migrainous patients containing 2,105 children, 658 siblings had migraine, 504 did not have it, and in 567 the history was not known or the children were too young. This gives an incidence of 67.2 per cent of the 1,538 children about whom data were available.

9. In 163 family histories given by children who did not have headache themselves, 90, or 11.8 per cent, of a total of 911 children are said to have migraine, 722 to be without migraine, and in 99 the history was not known.

The information about headache in parents and siblings secured from persons who did not themselves have headache, as in items 3 and 9, is probably not reliable. The figure in item 7 represents the same supposed error as recorded in item 4. The figures in items 5 and 6 might be changed on more accurate information about both parents.

The genetic and statistical evidence presented in this paper indicates that migraine is inherited as a dominant unit mendelian character.

EFFECT OF ADMINISTRATION OF MEDICINAL IRON ON THE IRON RESERVE

AN EXPERIMENTAL STUDY *

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In a previous publication [1] we gave the results of some experiments on the iron reserve in animals, first as affected by the standard casein diet, and second as affected by the feeding of food known to be rich in available iron. While it is commonly stated that the body does not have any reserve of iron in the same sense that it has reserves of calcium and phosphorus, there are many clinical facts which make it seem likely that there must be at least enough iron in reserve to take care of the ordinary contingencies of everyday life. Relatively prompt recovery of animals and human beings after bleeding, even when the iron in the diet is not especially abundant, would seem to make this point apparent. The experiments referred to were undertaken with the idea of determining in a positive manner whether this surmise is correct, and whether an iron reserve really does exist, and if so to obtain at least an approximate idea of the amount of such a reserve, and of the readiness with which it may be drawn on for the repair of losses of iron such as occur in hemorrhages. Since the present work is a direct extension of our previous experiments, a brief synopsis of the results of these will be here given.

Our plan of procedure was as follows: A large number of white rats was obtained and divided into two groups in such a way that the litters were divided, half of the young being in one group, and the other half being used as controls. One group was kept on the standard casein diet, the other group on the same diet, which was modified, in that a portion of the protein was obtained from dried beef liver instead of casein, the caloric and protein content of the whole remaining the same. Both of these diets were adequate in all respects. We have numerous charts which show that the growth curve was entirely normal. The young were reared successfully, the litters were full sized and the young in their turn grew normally, bred at the usual time and in their turn reared full sized litters of normal young. The hemoglobin content was

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1. Williamson, C. S., and Ets, H. N.: The Problem of the Iron Reserve, Arch. Int. Med. **40**:668 (Nov.) 1927.

determined immediately before the rats were placed on the diets, and then at intermediate times, after they had been on the diets up to four months.

Before the experiments were begun, the two groups showed practically identical concentrations of hemoglobin, namely 0.77 for the group to be placed on liver diet and 0.766 for the control group. After the animals had been on their respective diets for a little more than three months, the percentage of hemoglobin had increased materially in both groups, as is normally the case with young animals. The figures were 1.11 and 1.091. It is clear, then, both from these figures and from our previous work that the feeding of normal young rats with a diet which contains available iron in amounts far above their metabolic needs does not increase the amount of hemoglobin in the blood. This, in view of what is known of the constitution of the blood, was to be expected. Our train of thought was as follows. If the body is capable of storing up iron outside of the circulation, in a form available for use when there is a drain on the circulating iron, for instance, after hemorrhage, it would follow that if these two groups of animals were each bled identical amounts, the animals which had been fed on food rich in iron might recover from the effects of these hemorrhages more quickly than the animals on ordinary diets. Conversely, if, after the two groups had been bled to the same extent, one group should recover more quickly or to a greater extent than the control group, this fact would constitute the best possible proof that an iron reserve had been stored up and was capable of being used in the replacement of the lost blood. Our results in these experiments were striking and decisive. We began, as already stated, with identical concentrations of hemoglobin in both groups; six days after bleeding, we found that the group on the liver diet showed a concentration of 0.927, whereas the control group, on the casein diet, showed a concentration of only 0.745. At the end of twenty-eight days after bleeding, the group on the liver diet showed a concentration of 1.033, whereas the group on the casein diet showed only 0.735. These results were so striking as to admit of only one interpretation, namely that there is a definite storage of iron in a readily available form amounting, under our conditions of experiment, to about 30 per cent. These results were further checked by determinations of iron in the liver and spleen in groups of twenty animals on each diet before bleeding and after bleeding. Before bleeding the rats on the liver diet showed 22.2 mg.[2] of iron in their livers, and 51.2 mg. of iron in the spleen as compared with 14.2 and 21.3 mg. in the animals fed on casein. Determinations of iron in the liver and spleen were also

2. All values of iron are expressed in milligrams of iron per hundred grams of tissue.

made twenty-eight days after bleeding, with the following results: liver, 13.3 mg.; spleen, 29.5 mg. in the animals fed with liver, as compared with 9.9 and 14.1 mg., respectively, in the group fed with casein. By subtracting the figures after bleeding from those obtained before bleeding, it is plain that the animals on the liver diet lost 8.9 mg. from their livers and 21.7 mg. from their spleens, as compared with 4.3 and 7.2 mg., respectively, in the animals on the casein diet. These figures demonstrate conclusively, we think, not only that the storage is largely in the liver and spleen, but that these organs store the iron in a readily available form. Of course, it is possible, indeed probable, that much of the iron in these two organs is present in a form not available for conversion into hemoglobin. Our [1] previous experiments seem to show this clearly.

If it is accepted, then, as a demonstrated fact, that there is a substantial reserve of available iron in the organism which may amount, under conditions of experiment similar to ours, to as much as 30 per cent, then the further question naturally suggests itself, Is it possible to produce a reserve supply of available iron by the systematic feeding of ordinary medicinal iron in the place of the iron in the food?

It need hardly be pointed out that the matter is one of considerable practical, as well as theoretical, importance. In view of the admitted difficulties in the way of arranging a diet either for children or for adults, which contains a sufficiency of available food iron, it would be a tremendous help if the ordinary forms of medicinal iron could take the place of this food iron in building up a reserve. If it should prove that medicinal iron were even measurably efficient in storing up a reserve of available iron we could, perhaps, afford to give less thought to the diet, at least so far as its containing a sufficient amount of food iron is concerned.

METHODS

Our experiments were conducted along the same lines as those followed in the work already mentioned. A large number of young, white rats was obtained in litters of from six to ten. The litters were so divided that half of the animals in each litter were used for the iron feeding experiments, while the other half were used as controls. We feel that it is most important to use a large number of animals, and to use as many controls as there are animals to experiment with. This is a point that is too often overlooked in such work. Our plan of procedure was as follows. The concentration of hemoglobin of the blood was taken before the rats were placed on the diet, which was identical in the two groups, except that in one, which we called the "iron diet group" we added ferric citrate. After the animals had been on their respective diets for ninety days, the concentration of hemoglobin was again taken. Immediately after the second determination, each animal was bled 25 per cent of the calculated volume of blood directly from the heart. The concentration of hemoglobin was then again taken on each animal on the sixth and twenty-eighth day after it had been bled. It is not necessary to refer in detail to the methods employed, since they have been described at length

TABLE 1.—*Results of Experiments on White Rats*

Rat Number	Rats on Iron-Free Diet				Rat Number	Rats on Iron Diet			
	Before Bleeding		After Bleeding			Before Bleeding		After Bleeding	
	June 27	Sept. 27	6 Days	27 Days		June 27	Sept. 27	6 Days	27 Days
3	0.921	1.236	0.999	1.188	1	0.915	1.149	1.068	1.049
7	0.946	0.968	0.895	0.934	2	0.842	0.891	0.992	1.004
8	0.938	1.078	1.032	1.239	5	0.955	0.907	0.838	.....
9	0.834	0.911	0.652	0.983	6	1.004	1.180	0.632	1.049
10	0.858	1.093	0.957	1.191	11	0.790	1.104	1.032	1.029
15	0.692	0.942	1.032	1.083	12	0.999	1.066	1.039	0.988
18	0.899	1.051	0.756	1.052	13	0.906	1.039	0.968	1.013
22	0.838	1.004	0.768	1.008	14	0.929	0.934	1.034	0.962
26	0.936	1.051	0.903	1.086	16	0.951	0.992	0.701	0.939
31	0.845	1.058	0.645	1.039	17	1.006	0.878	0.897	1.160
33	0.999	1.076	0.870	1.168	19	0.923	1.215	1.073	1.025
34	0.942	1.066	0.864	1.218	20	1.039	1.004	0.689	0.988
35	0.951	1.025	0.862	0.990	21	0.907	1.135	0.946	1.051
36	1.044	0.966	0.921	1.018	23	0.955	1.056	0.842	1.103
38	1.109	0.938	0.741	1.071	24	1.015	1.149	0.946	1.032
40	1.039	0.891	0.768	0.953	27	0.997	1.013	0.970	0.964
43	0.955	1.163	0.756	1.083	28	0.921	1.124	1.022	1.135
44	0.921	1.086	0.995	1.206	32	0.900	0.940	0.946	0.891
46	0.917	1.044	0.834	1.093	37	0.927	1.060	0.822	1.025
49	0.905	1.119	0.944	1.242	39	0.807	1.027	0.932	1.010
52	0.780	1.036	0.751	1.053	41	0.923	1.223	1.001	1.020
55	0.966	1.109	0.913	1.135	42	1.010	0.981	0.809	1.078
57	0.923	1.093	0.847	1.046	45	0.934	1.078	0.842	0.802
58	0.921	1.098	0.923	1.141	47	0.813	0.938	0.911	0.881
60	0.938	1.053	0.979	1.182	53	0.885	1.041	0.683	1.006
61	1.051	0.988	0.798	1.239	54	0.883	0.961	0.966	1.127
62	1.006	0.713	0.849	1.043	56	0.988	1.093	0.921	1.141
64	1.081	1.041	0.915	1.160	63	1.081	0.847	1.049	1.223
65	0.944	1.068	0.891	1.143	66	0.901	1.073	0.990	1.146
68	1.046	1.053	0.957	1.185	67	0.966	1.093	0.678	1.034
70	0.968	1.135	0.925	1.125	69	0.940	1.114	0.988	0.992
72	0.907	1.122	0.990	1.165	71	0.955	1.088	1.053	1.091
73	0.938	0.860	0.895	1.149	77	0.956	1.076	0.921	1.032
74	0.983	1.061	0.713	1.010	78	0.949	0.936	0.940	1.041
75	0.986	1.270	1.010	1.071	79	0.909	1.008	1.049	1.119
76	0.927	1.053	1.027	1.111	81	1.111	1.078	0.946	.....
80	1.011	0.813	0.867	.....	84	0.979	1.011	0.887	0.955
83	0.944	1.103	1.001	1.068	86	1.044	1.114	0.864	0.968
87	0.990	0.907	1.055	1.122	88	1.053	0.858	0.997	0.988
91	0.955	1.163	1.027	1.177	89	1.029	0.909	0.932	1.061
92	0.796	1.039	1.018	1.182	90	0.938	1.073	0.938	0.998
93	0.967	0.953	0.716	1.220	96	0.938	1.093	0.944	0.992
94	0.885	1.038	0.955	1.141	97	1.032	1.048	0.662	0.878
100	0.953	1.165	0.853	1.071	98	0.936	1.138	0.936	1.098
101	0.903	1.130	0.889	1.036	99	0.953	1.191	0.911	0.999
103	0.964	1.100	0.719	1.081	102	0.905	1.103	0.656	1.086
107	0.802	1.146	0.961	1.101	104	0.921	1.036	0.953	1.053
108	0.915	1.148	0.962	0.942	105	0.979	1.046	0.856	0.889
109	0.997	1.083	0.961	1.006	112	0.866	1.034	0.905	0.903
111	0.813	1.034	0.756	0.949	114	0.903	1.049	0.934	1.024
115	1.138	1.117	0.774	0.919	116	0.936	1.015	0.929	1.029
118	1.004	1.093	0.939	1.233	117	0.860	1.057	0.834	1.138
123	0.936	1.068	0.821	1.027	119	0.851	1.133	0.891	1.163
132	0.936	1.163	1.029	1.101	121	0.944	1.117	0.992	1.106
135	0.868	0.899	0.877	0.860	122	0.923	1.041	0.923	1.044
143	1.001	0.887	0.730	1.174	125	0.944	1.039	0.748	1.018
144	0.975	0.990	0.864	1.109	128	0.836	1.063	0.925	1.036
150	0.959	1.029	0.891	1.044	130	1.018	1.051	0.905	0.955
153	0.849	1.029	0.855	1.168	131	0.921	0.997	0.944	1.049
154	0.887	1.141	0.842	1.053	133	0.940	1.106	0.809	.....
156	0.940	0.956	0.879	0.855	134	0.889	0.940	0.816	0.874
159	0.853	1.039	0.872	1.138	136	0.942	1.093	0.979	1.013
161	0.955	1.116	0.805	1.106	138	1.081	1.041	0.769	0.899
162	0.874	1.101	0.778	1.041	141	0.997	1.053	0.949	1.038
164	1.024	1.093	0.951	1.119	145	0.949	1.083	0.797	0.997
165	0.907	1.029	0.882	1.094	146	0.990	1.044	0.953	1.088
166	0.883	1.135	0.816	1.041	151	0.960	0.919	0.895	0.829
169	0.919	1.098	0.889	1.071	155	0.863	0.983	0.698	0.795
171	0.903	1.146	0.880	1.071	157	0.975	0.895	0.788	0.864
175	0.981	0.932	0.711	1.088	158	0.961	0.938	0.665	0.879
177	0.864	1.098	0.911	0.990	160	1.039	1.013	0.944	1.105
179	0.975	1.114	0.919	1.114	168	1.063	0.917	0.708	0.883
180	0.931	1.114	0.953	1.101	172	0.957	1.024	0.891	1.034
181	0.979	1.020	0.847	0.997	173	0.856	1.044	0.903	0.917
183	0.911	0.946	0.725	0.849	174	0.919	1.071	0.842	1.063
184	0.949	1.124	0.866	1.066	176	1.046	1.076	0.903	1.001
186	0.923	0.934	0.602	0.979	178	0.849	1.032	0.842	0.942
187	1.015	1.073	0.955	1.182	182	0.928	1.044	0.741	0.929
192	0.878	1.168	0.876	1.081	185	0.972	0.823	0.681	0.600
...	.....	.....	.....	.....	188	0.983	1.044	0.905	1.013
...	.....	.....	.....	.....	190	0.975	1.049	0.876	1.049
...	.....	.....	.....	.....	191	0.999	0.990	0.864	0.934
Average	0.934	1.051	0.874	1.084	Average	0.945	1.035	0.885	1.005

in a previous communication.[3] We adopted in this work, as before, the accurate spectrophotometric method, since it requires a minimal amount of blood, does not have any color standards to fade, and, if one has the proper command of the technic and a suitable apparatus, admits of an exceedingly accurate and fairly rapid determination of hemoglobin.

RESULTS

Our results can be stated in a few words. The average concentration of hemoglobin of the rats before being placed on the diet was 0.934 for the controls and 0.945 for the group to be placed on an iron diet. After the rats had been on the diets for ninety days, the concentration of hemoglobin was 1.051 and 1.035 for the controls and for the rats fed on iron, respectively. Such variations as these, amounting to 1 or 2 per cent, occur in any series of animals, even when on identical diets. We have then again abundant confirmation of our previous results, namely, that it is not possible to increase the amount of hemoglobin in the blood in normal, young rats by feeding them ferric citrate in addition to their standard diet.

On the sixth day after bleeding, we found that the concentration of hemoglobin was 0.874 and 0.885 for the controls and the groups fed on iron, respectively. In other words, the two groups were substantially identical. To make sure that there might not be a belated improvement, we again took the concentration of hemoglobin on the twenty-eighth day after bleeding, and found the concentrations to be 1.084 for the controls and 1.005 for the group fed on iron. The question may arise as to whether a difference of approximately 8 per cent is within the probable limit of error, but in any event it is to the disadvantage of the group fed on iron. From these figures, then, it will seem perfectly obvious that it is not possible by the administration of ferric citrate over a relatively long period of time to build up reserve of available iron, that is of iron capable of being converted into hemoglobin. We did not make analyses of either the entire bodies of the rats or the livers or spleens, since we had done this and had published the results in detail in a previous communication,[3] and had shown conclusively that there is a storing up of iron in the liver, spleen and bone marrow, but that, under our conditions of experiment, this iron was not capable of being converted into hemoglobin. The fault lies not with the absorption of iron, as was supposed by Bunge and his followers, but with its ability to be converted into hemoglobin.

The results obtained in the experiments just quoted stand in the most striking contrast to the results obtained under identical conditions in the group of animals which had been fed on food iron in quantities above their metabolic needs. As already stated, there was, in this group,

3. Williamson, C. S., and Ets, H. N.: Value of Iron in Anemia, Arch. Int. Med. **36**:333 (Sept.) 1925.

a storage of available iron to the extent of about 30 per cent. For the sake of clearness and easy comparison, the results are shown side by side in table 2.

An inspection of table 2 shows that whereas in the rats fed on food iron and on ferric citrate the concentration of hemoglobin was substantially identical in both the experimental and the control groups before they had been bled, on the sixth day after bleeding the ratio of the concentration in the group fed on ferric citrate was $\frac{0.885}{0.874}$, i.e., substantially identical, whereas in the animals fed on food iron, the ratio was $\frac{0.927}{0.732}$, a difference of more than 20 per cent. On the twenty-eighth day after bleeding, in the animals fed on ferric citrate, the ratio was $\frac{1.005}{1.084}$, an actual diminution, whereas in the rats fed on food iron, the ratio was $\frac{1.033}{0.785}$, a striking increase in favor of the animals fed on food iron.

TABLE 2.—*Comparison of Results with Food Iron and Ferric Citrate*

	Results with Ferric Citrate				
	Before Being Placed on Diet	After Ninety Days on Diet	Bled 25 Per Cent of the Volume of Blood	Six Days After Bleeding	Twenty-Eight Days After Bleeding
Iron group	0.945	1.035	.....	0.885	1.005
Control group	0.934	1.051	.....	0.874	1.084
	Results with Food Iron (Liver) in Excess				
Liver group	0.770	1.104	.....	0.927	1.033
Control group	0.766	1.096	.....	0.732	0.785

We may say, then, that it is readily possible for the organism to store a satisfactory reserve of iron, if there has been an excess of available food iron in the diet for a sufficient time. These results cannot be obtained by the simple addition of ferric citrate, however desirable this might be.

It cannot be definitely concluded that if the addition of ferric citrate cannot build up a reserve of available iron in a normal animal, it will not build up the concentration of hemoglobin in an animal which has a pathologically low concentration of hemoglobin. It is, however, most suggestive, and taken in combination with our previous work, we are inclined to see a confirmation of that work.

SUMMARY

1. Rats fed on the standard diet plus ferric citrate do not show an increase in the concentration of hemoglobin over rats on the same diet minus ferric citrate.

2. After 25 per cent of the volume of blood has been bled, rats which have been fed ferric citrate in addition to the standard diet for a long

time before bleeding do not recover any more quickly than the control group which has not been given ferric citrate. Expressed in other words, the addition of ferric citrate to the diet of rats cannot build up a reserve of available iron, that is, of iron capable of being converted into hemoglobin.

3. This last result is in striking contrast to the results of our previous work, wherein it was shown that the feeding of food iron under the same conditions resulted in the storing up of approximately 30 per cent of reserve iron, which was immediately utilizable after a strain on the body, as, for example, after hemorrhage.

Book Reviews

TRATADO DE LA DIABETES. By PEDRO ESCUDERO. Pp. 700. Buenos Aires: Libreria "El Alteneo," 1927.

This book of about 700 pages covers the extent of the modern knowledge of diabetes. It is arranged in an orderly manner and treats thoroughly involved features of the chemistry of sugar metabolism. The presentation is clear and simple. It is not only a textbook for the student, but a handy reference book, the technic of all the necessary tests and chemical reactions being described throughout.

The material for this treatise comes from the large clinic of Escudero, who is professor of medicine in the University of Buenos Aires, and the result of much practical experience can be found in these pages.

The work is divided into four sections. The first section contains an elaborate discussion of sugar metabolism and its chemical features in both the normal and the diabetic person. Under this heading is included the relation of sugar metabolism to other foodstuffs, and the importance of the broader aspects of alimentation in diabetes is emphasized.

Section two covers the pathologic, physiologic and clinical aspects of glycosuria. In this section the portions dealing with the use of insulin are especially valuable.

The third section takes up the complications of diabetes and their management. Especially noteworthy here is the original work of Escudero on latent diabetes. He has shown that a number of diseases of the skin, the eyes and the nervous system are due to lack of power of oxidation of carbohydrates, which has not yet reached the stage of glycosuria. By careful studies of the metabolism of a number of such conditions and antidiabetic management he has brought about striking clinical cures.

The fourth section should really be published as a separate pamphlet. It is a "Guide for the Diabetic," and begins with a short description in simple terminology, that is comprehensive to the laity; it continues with the usual instructions for the patient as to his mode of life and dietary lists. This section is not of much value to the American public as so many of their foods are strange to us.

THE SIMPLE GOITRE. By ROBERT MCCARRISON. Price $4.00. New York: William Wood & Company.

The contents of this book formed the subject matter of a report to the International Conference on Goiter held at Berne in August, 1927.

In the introduction, he discusses the normal physiology of the thyroid and its response to heat, cold, altitude, puberty and other factors, and emphasizes here as throughout the book that too much stress has been laid on deficiency of iodine as the dominant factor in enlargement of the thyroid of the adenomatous type. The two types of simple goiter—adenoma parenchymatous and diffuse colloid—he believes differ in their epidemiology and etiology. Deficiency of iodine may play an important rôle in colloid goiter. His studies, made in India, were almost entirely on the adenoma parenchymatous type. He believes deficiency of iodine is not the important etiologic factor. His experimental work on both animal and man, all of which has been previously published, suggests the presence of some toxic substance, probably bacterial. His clinical observation and experimental work were apparently carefully controlled and while his views have not been widely accepted, they are nevertheless convincing, and cannot be lightly discarded.

The last half of the book is given over to illustrations. There are charts showing the incidence of goiter before and after purifying the water supply, photographs of people with goiter and creatins, photographs before and after production of experimental goiter in man, another series showing the result of

treatment with intestinal antiseptic or protein shock therapy, and finally a series of photomicrographs of the thyroid in man and experimental animals. This volume, which contains the collected observations of a lifetime, is a valuable contribution concerning one man's experience with goiter.

HORMONE UND INNERE SEKRETION. By DR. FRITZ LAQUER, Privatdozent an der Universität Frankfurt A.M. Price, 8.30 marks, paper; 10 marks, bound. Pp. 136, with index. Dresden and Leipzig: Theodor Steinkopff, 1928.

In the plethora of monographs on the endocrine glands that are being published today, this short monograph of Dr. Laquer ranks among the best from the point of view of brevity and reliability. The author has succeeded in an admirable manner, and with rare judgment, in selecting and organizing the known facts in this important field. Hypotheses and vagaries are largely excluded. The author does not attempt, and it would be impossible in the few pages of this book, to treat in extenso the organotherapeutic aspect of the endocrine glands; the histologic aspects are also largely eliminated. It is essentially an excellent summary of the biochemical and the physiologic knowledge of the endocrine glands. As an index of the author's admirable judgment and scientific caution, a group of glands and substances are treated briefly in the last chapter under the general heading of "Hormones of Hypothetical Nature." Here the author includes the pineal body, the so-called heart hormone of Loewi, the spleen, the liver, the salivary glands and cholin. At the end of the book is an appendix which contains a bibliography of 1,200 titles arranged under the subject matter of the chapters of the book.

THE NEW YORK ACADEMY OF MEDICINE LECTURES ON MEDICINE AND SURGERY. First Series. Price, $5. 309 pages, with 39 illustrations. New York: Paul B. Hoeber, 1927.

In the preface the following statement appears, "The first series of Practical Lectures for the general practitioner arranged by the Committee on Medical Education and given at The New York Academy of Medicine in 1926-1927 met with such favor that the lectures are now published in book form in the belief that they will meet a need which is felt by the profession generally."

This series of fifteen lectures on a variety of general topics does not add anything new to medical literature, but the subjects are presented in a practical and popular style. To me the chapters on "The Treatment of Cardiovascular Syphilis" by Harlow Brooks, "General Infection by Bacteria" by Emanuel Libman, "The Cutaneous Manifestations of Syphilis" by George N. MacKee, "Surgical Aspects of Diseases of the Thyroid" by Eugene H. Pool, and "The Treatment of Pneumonia" by David Riesman, are of particular interest. Others may be more attracted by that on "Clinical Aspects of Common Otological Infections" by Samuel J. Kopetzky; by "Remarks on Eye Conditions" by John M. Wheeler; or by "Obstetrical Problems in General Practice" by J. O. Polak. The chapters on pathologic causes of "Human Misconduct" by Max Schlapp, "The Problems of the Child's First Year" by H. B. Wilcox, and "Contagious Diseases" by Shirley W. Wynne are very good.

The general practitioner will doubtless find these lectures both interesting and profitable.

TRAITE DE PHYSIOLOGIE, NORMALE ET PATHOLOGIQUE. Par G. H. ROGER, Professor of Physiologie à la Faculté de médecine de Paris, Doyen de la Faculté. Tome III. Physiologie du Foie et de L'Appareil Urinaire. Price, 85 francs. Pp. 751. Tome IV. Les Secretions Internes. Price, 80 francs. Pp. 858. Paris: Masson & Cie, 1928.

These two volumes maintain the elements of excellence as well as the elements of defects already pointed out in the previous volumes of this large set. The chapter on the liver by Dr. Roger is on the whole excellent; so are the chapters on the kidneys by Dr. Rathery and Dr. DuBois.

In volume IV, dealing with the endocrine glands, the best chapters are those on the pancreas, insulin and diabetes by Dr. E. Hédon and Dr. L. Hédon, and the chapter on the hypophysis and the basal region of the brain by Dr. Roussy and Dr. Gournay. Dr. Hédon and Dr. Roussy have done valuable experimental work in their fields, and this has given tone and critical judgment to their presentation. The ovaries and testes are not treated in this volume. As an example of extreme plethora of words which in general tend to weaken many chapters of this volume, the chapter on the pineal gland by Dr. Laignel-Lavastine might be referred to. The chapter runs up to nearly fifty pages and at the end the author concludes that the pineal body is really an endocrine organ, a conclusion highly problematic today. The reliable data on the physiology and pathology of the pineal gland can certainly be condensed to less than fifty pages with profit.

THE MECHANICS OF THE DIGESTIVE TRACT. By WALTER C. ALVAREZ, M.D., Associate Professor of Medicine, University of Minnesota (Mayo Foundation). Second edition. Price, $7.50 net. Pp. 428. New York: Paul B. Hoeber, 1928.

This book is intended as an introduction to gastro-enterology, but it can be read with profit by those who have worked long in this field and by all who are endeavoring to solve the problems which it presents to the physiologist or to the clinician. The second edition is practically a new book, thoroughly up-to-date. Its scope is much wider than that of its predecessor, which was devoted chiefly to the author's gradient theory. The practical application of modern physiologic discoveries is kept constantly in mind, and every effort is made to correlate them with the known clinical facts. Considerable attention is given to the alterations in function produced by disease or by operative procedures. Recent work on the gallbladder is carefully reviewed and attractively presented in the chapter on "The Mechanics of the Gallbladder." One of the most interesting portions to the internist is that devoted to flatulence, because the author has gathered together much important data regarding this common symptom.

Many readers will be pleased to find in the book pictures of numerous men who have been or are outstanding figures in the field of gastro-enterology.

The bibliography of nine hundred titles is worthy of real praise.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR: TRAINING. Volume 7. Price, $3.25. Washington, D. C.: Government Printing Office, 1927.

The 1,200 pages of this volume do not make light reading. It is a heterogeneous hodgepodge of data which the reviewer can see no reason in the world for publishing. Nearly half of the book is made up of an appendix, in fine print, and contains documents of every conceivable character, ranging from descriptions of visits to the front by student officers, to lectures on various branches of science delivered in army training camps.

The body of the work consists of detailed plans and histories of the various training centers. Daily curriculums and courses of study follow each other, page after page, with distressing monotony.

A study of the work after the lapse of ten years since the war leaves in the reviewer's mind several queries. The first is as to the wisdom of trying to make such good soldiers out of physicians. The second is the obvious absurdity of attempting to make administrators out of all the more prominent scientists.

As a reference work for the unlucky persons who will have to organize a medical service for the next war, volume 7 will be of great value, but it does not make a very readable contribution to the present series.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY, VOLUME 12. Part 1, Physical Reconstruction and Vocational Education. Part 2, The Army Nurse Corps. Price $3. Washington, D. C.: Government Printing Office, 1927.

Part 1, gives in detail the objective and methods of carrying out the physical restitution of the soldiers. Previous to the armistice, an effort was made to

rehabilitate as many as possible for a return to active duty; following the armistice, to rehabilitate and when necessary to give vocational training in order that soldiers might be enabled to maintain a livelihood in civilian life. The methods by which this was attempted are given in detail.

Part 2 discusses the activities and, one might say, the hardships, especially of the overseas nurse.

UEBER EIRVEISBESCHRANKUNG IN DER BEHANDLUNG DES DIABETES GRAVIS. By KARL PETEIN, head of the Department of Medicine, University of Lund (Sweden) and S. LANG, Karlsbad, Germany. Pp. 72. Verlagsbuchhandlung: Carl Marhold, 1927.

The discovery of insulin made it necessary to publish a second edition of this book, the first appearing in 1922. Petrin uses the high fat and low protein diet, which is known as the Newburgh diet in this country. The good results are explained by Snapper's (Amsterdam) work on the secretory function of the kidney. By giving the kidney a rest from the secretion of nitrogen waste products, it is easier to take care of the beta oxidation of oxybuteric acid, diacetic acid and acetone. In this way, acidosis is prevented. Insulin, he believes, should be used only in coma and when the blood sugar does not come down to normal when the patient is on a maintenance diet.

KRANKHEITSLEHRE DER GEGENWART STRÖMGUNGEN UND FORSCHUNGEN IN DER PATHOLOGIE SEIT 1914. WEISENSCHAFTICHE FORSCHUNGSBERICHTE—NATURWISS. REIHE, BAND XVII. By GOTTHOLD HERXHEIMER, Head of Department of Pathology of the General Hospital of Weisbaden, Germany. Price, 12 marks, unbound. Pp. 256. Dresden: Theodor Steinkopff, 1927.

This volume is an excellent review of the new ideas and discoveries in pathology since 1914. There are good references to every subject. The author regrets that most of the references are in German, but because of the tremendous literature this was unavoidable. Over 10,000 books and papers have been reviewed. This is a valuable asset to any medical library.

DIABETIC MANUAL FOR PATIENTS. By HENRY J. JOHN. Price, $1.75. St. Louis: C. V. Mosby Company, 1928.

This new manual is simply and intelligently written and gives an excellent presentation of the general principles underlying the disease, diabetes, and its management from the layman's point of view, although a great deal of interesting medical statistics is included. There are numerous charts presented in attractive fashion. Of special interest are the color illustrations of the various ordinary foods, giving their composition in graphic manner. The usual diabetic recipes follow in the rear of the book as an appendix. This manual will take its place with the best of its kind in American literature. It is pleasant to notice that the author refers to the manuals already in existence as reading matter recommended for patients.

THE INTERNATIONAL MEDICAL ANNUAL. Price, $6.00. Pp. 573. New York: William Wood & Co., 1928.

This is the forty-sixth year this book has been published, and the manner of treating the progress in medicine over the past year does not differ from the previous volumes. It summarizes very well the recent work in medicine, surgery and the specialties. References are given for more detailed data. The contributors are all English.

The book is of great value to anyone who does not find time to keep up with the medical literature, or who wishes quickly to summarize the most recent work in the treatment of disease.